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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 30-April-1999

SUBJECT: PP# 7F04854. Sulfosate in/on Soybeans and Animal Commodities. **HED Risk Assessment**. Chemical#: 128501. DP Barcode: D243318, D254804. Case #: 289000. Submission #: S526352.

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The Health Effects Division (HED) of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The Registration Division (RD) of OPP has requested that HED evaluate toxicology and residue chemistry data and conduct dietary, occupational/residential and aggregate risk assessments, as needed, to estimate the risk to human health that will result from the use of sulfosate in/on soybeans and ruminants.

A summary of the findings and an assessment of human risk resulting from the proposed use of sulfosate are provided in this document. The hazard assessment was provided by Jessica Kidwell of Registration Action Branch 1 (RAB1), the residue chemistry data review and the dietary risk assessment by George Kramer and Susie Chun of RAB1, and the occupational/residential review by Dana Vogel of RAB1.

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1.0 EXECUTIVE SUMMARY

HED is conducting a human health risk assessment for sulfosate in support of the establishment of permanent tolerances on soybeans and animal commodities. HED has evaluated toxicology and residue data for sulfosate submitted by Zeneca. **The data are adequate to support a conditional Section 3 registration and the establishment of permanent tolerances on soybeans and animal commodities.**

Sulfosate (the trimethylsulfonium salt of glyphosate, also known as glyphosate-trimesium) is a 1:1 molar salt of N-(phosphonomethyl)glycine anion (PMG) and the trimethylsulfonium cation (TMS). It is a nonselective systemic herbicide which is active against a broad range of weeds and is being developed for agricultural use in a wide range of crops. The Agency recently established permanent tolerances under 40 CFR §180.489(a) to replace time-limited tolerances that had been established under 40 CFR §180.489(b) (62 FR 48597, 09/11/98). At the same time, tolerances that had been established under 40 CFR §185.5375 were moved to §180.489(a). The permanent tolerances were established for the following commodities: aspirated grain fractions; forage, stover, and grain of field corn; stover and grain of popcorn; prune; raisins; forage, hay, seed, and hulls of soybeans; fat, meat, and meat byproducts of cattle, goats, hogs, horses, and sheep; milk; fat, meat, meat byproducts (except liver), and liver of poultry; and eggs.

For this action, amended labels have been proposed for use of sulfosate formulated as Touchdown®, 6 lb/gal SC formulation (57.6% a.i.), EPA Reg. No. 10182-324, and Touchdown® BTU, 5 lb/gal SC formulation (48.6% a.i.), EPA Reg. No. 10182-429, to add a preharvest use and to add uses on glyphosate-tolerant soybeans. The amended use will also affect tolerances for residues in meat and milk and proposed tolerances for poultry and eggs.

Broadcast applications can be made before, during, or after planting, but prior to crop emergence. The Touchdown® products can also be applied to soybeans as a spot spray, preharvest broadcast spray, or by wiper/wick. Spot treatments must be made 8 weeks prior to harvest and preharvest applications must be made a minimum of 7 days before harvest. There are currently no registered uses of this chemical in residential situations.

This action is in response to a label amendment for Touchdown® and Touchdown® BTU. The maximum application rate and methods of application have not changed. Therefore, since the exposure assessment for sulfosate on soybeans has already been done (Memo, M. Copley, G. Kramer, J. Cruz 7/10/98; DP Barcode D242550), there is no need to reassess worker exposure. Therefore, no occupational exposure assessment is required.

Hazard Assessment

The acute toxicity data for sulfosate technical show that this chemical is not acutely toxic by the oral, inhalation, and dermal routes of exposure [Toxicity Categories III and IV]. It is a mild skin and eye irritant and a slight dermal sensitizer. Sulfosate is a neurotoxic chemical. Evidence of

neurotoxicity was seen in several studies in rats, dogs, and mice. Signs of neurotoxicity included Functional Observation Battery (FOB) effects in rat neurotoxicity studies and treatment-related salivation and emesis in the dog following subchronic and chronic exposures. Salivation was the most consistent sign, and in dogs may have served as a precursor to more severe symptoms. Dogs appear to be the most sensitive species for these effects, with high intra-individual variability in sensitivity. There were also concerns for hydrocephalus in all dog studies and possible treatment related histopathology in the mouse carcinogenicity and 21-day dermal rat studies. Developmental toxicity studies in rats and rabbits and a two-generation reproduction study in rats provided no indication of increased susceptibility in rats or rabbits from *in utero* and/or post natal exposure to sulfosate. Based on the available mutagenicity studies, there are no concerns for mutagenicity at this time. Sulfosate is classified as a "Group E" chemical (no evidence for carcinogenicity in humans).

Dose Response Assessment

On June 12, 1998, the Hazard Identification Assessment Review Committee (HIARC) met to re-examine the neurotoxicity hazard assessment/characterization for sulfosate. This was a follow-up to the HIARC meeting held on April 26, 1998, which met to re-assess the Reference Dose (RfD) established in 1994 and select the toxicological endpoints for acute dietary as well as occupational exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to sulfosate as required by the Food Quality Protection Act (FQPA) of 1996. Based on the weight-of-evidence for concerns of neurotoxicity, the HIARC recommended the requirement of a developmental neurotoxicity study with sulfosate to evaluate the potential for effects on functional development.

The FQPA Safety Factor Committee (SFC) met on June 29, 1998 and determined that the data indicate that there is no increased susceptibility to young rats or rabbits following *in utero* exposure in prenatal studies or in the postnatal study in rats. However, the FQPA SFC recommended that the FQPA Safety Factor should not be removed, instead it should be reduced to 3x, because of the need for a developmental neurotoxicity study to characterize the observed neuropathology in the subchronic and chronic studies.

For acute dietary exposure, the HIARC selected an acute RfD of 1.0 mg/kg (no observed adverse effect level (NOAEL) = 100 mg/kg, UF = 100). The acute RfD is based on an acute neurotoxicity study in the rat where mortality, decreased body weight and food consumption, and clinical signs of neurotoxicity were seen at the LOAEL of 300 mg/kg. For chronic dietary exposure, the HIARC selected a chronic RfD of 0.10 mg/kg/day (NOAEL = 10 mg/kg/day, UF = 100). The chronic RfD is based on a one year feeding study in dogs where emesis and salivation were seen at the LOAEL of 50 mg/kg/day (HDT). The FQPA safety factor of 3x is applicable for All Populations which include Infants and Children, resulting in an acute population adjusted dose (aPAD) of 0.333 mg/kg/day and a chronic population adjusted dose (cPAD) of 0.0333 mg/kg/day.

Dietary/Aggregate Risk Estimates

Aggregate risk assessments are limited to food and water since there are no residential uses for sulfosate that will result in post-application residential exposure.

Acute risk estimates associated with aggregate exposure to sulfosate in food and water do not exceed HED's level of concern. The Tier 1 acute dietary analysis for sulfosate is a highly conservative estimate of dietary exposure that assumes tolerance level residue values and 100 percent crop treated (CT). For the U.S. population, 10% of the aPAD is occupied by dietary (food) exposure. For the most highly exposed subgroup, Infants (< 1 year), 42% of the aPAD is occupied by dietary (food) exposure. Thus, the percent aPADs were below HED's level of concern at the 95th percentile for the U.S. population and all subgroups. The maximum estimated concentrations of sulfosate in surface water (211 ppb) and ground water (0.00377 ppb) are less than OPP's Drinking Water Levels of Comparison (DWLOCs) for sulfosate (2,000-10,500 ppb) as a contribution to acute aggregate exposure. (Note: In a previous risk assessment (07/10/98) for the use of sulfosate in/on corn, wheat, pome fruit, and soybeans, EFED provided ground water and surface water exposure estimates for sulfosate at a maximum annual application rate of 4.75 lbs a.i./acre (Memo, J. Carleton, S. Termes, 5/14/98; Barcode D243384, D2443314). To conduct the current risk assessment for the use of sulfosate on soybeans, HED estimated ground water and surface water exposures (both acute and chronic) using the values provided by EFED in the 5/14/98 memo and adjusting for the current maximum annual application rate of 8 lbs a.i./acre). Therefore, OPP concludes with reasonable certainty that residues of sulfosate in drinking water do not contribute significantly to the acute aggregate human health exposure and risk at the present time considering the present uses and the uses proposed in this action.

Chronic risk estimates associated with aggregate exposure to sulfosate in food and water do not exceed HED's level of concern. The Tier 3 chronic dietary analysis for sulfosate is a more refined estimate with the use of some **anticipated residues (ARs)** for soybean commodities and **%CT** information (for soybeans, oranges, grapefruit, corn, peaches, and wheat). For the U.S. population, 9% of the cPAD is occupied by dietary (food) exposure. For the most highly exposed subgroup, Children (1-6 years old), 26% of the cPAD is occupied by dietary (food) exposure. Thus, the percent cPADs were below HED's level of concern. The estimated average concentrations of sulfosate in surface water (20 ppb) and ground water (0.00377 ppb) are less than OPP's levels of comparison for sulfosate in drinking water (250-1,060 ppb) as a contribution to chronic aggregate exposure. Therefore, OPP concludes with reasonable certainty that residues of sulfosate in drinking water do not contribute significantly to the chronic aggregate human health risk at the present time considering the present uses and uses proposed in this action.

Recommendations for Tolerances

Adequate residue chemistry and toxicology data have been submitted to support the establishment of the following permanent tolerances for sulfosate as a result of the amended use:

Soybean, seed	21 ppm
Kidney*	6.0 ppm
Meat Byproducts* (except kidney)	1.5 ppm
Meat*	1.0 ppm
Fat*	0.5 ppm
Milk	1.5 ppm

Poultry Meat Byproducts	0.1 ppm
Poultry Meat	0.05 ppm
Poultry Fat	0.05 ppm
Eggs	0.05 ppm

* of cattle, hogs, sheep, goats, and horses

The residue chemistry, exposure and toxicological data bases are adequate to support permanent tolerances with a conditional registration for the use of sulfosate in/on soybeans and animal commodities in terms of human health risk. HED recommends that the petitioner be required to submit: 1) a developmental neurotoxicity study, 2) a revised Section F, and 3) a revised Section B.

To provide for the re-evaluation of the anticipated residues, the Agency will require under Section 408(b)(2)(E) that additional data be submitted within five years. The registrant must also submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether sulfosate shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for sulfosate need to be modified or revoked.

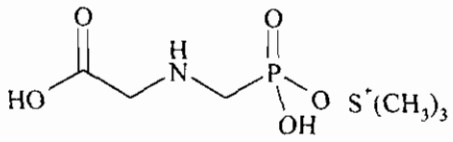
2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

Sulfosate (the trimethylsulfonium salt of glyphosate, also known as glyphosate-trimesium) is a 1:1 molar salt of N-(phosphonomethyl)glycine anion (PMG) and the trimethylsulfonium cation (TMS). It is a nonselective foliar systemic herbicide used to control a broad spectrum of emerged grass and broadleaf weeds. Sulfosate is similar in chemical structure, metabolic breakdown and proposed use to glyphosate.

2.1. Identification of Active Ingredients

Chemical Name:	Sulfonium, trimethyl-, salt with N-(phosphonomethyl)glycine (1:1)
Common Name:	Sulfosate
PC Code Number:	128501
CAS Registry No.:	81591-81-3
Empirical Formula:	$C_6H_{15}O_5SNP$
Molecular Weight:	244

2.2. Structural Formula (Sulfosate)



2.3. Physical and Chemical Properties

Product chemistry data were not submitted to HED in conjunction with the subject petitions. When sulfosate was first submitted for a nonfood use, the product chemistry was reviewed by RD and found to be adequate (Memo, K. Liefer, 3/17/87). There are no product chemistry data gaps (Letter, R. Taylor 2/15/89).

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

Sulfosate is a herbicide which consists of trimethylsulfonium glyphosate. The cationic component is trimesium and the anionic component is glyphosate. The toxicology database provides no evidence that sulfosate has anticholinesterase activity, as evidenced by decreased cholinesterase activity in rats and dogs following subchronic and chronic exposures.

The acute toxicity data for sulfosate technical show that this chemical is not acutely toxic by the oral, inhalation, and dermal routes of exposure [Toxicity Categories III and IV]. It is a mild skin and eye irritant and a slight dermal sensitizer. Table 1 summarizes the acute toxicity of sulfosate technical.

Table 1. Summary of Acute Toxicity of Sulfosate Technical

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral - Rat	00126608, 00132172	LD_{50} = 748 mg/kg	III
81-2	Acute Dermal - Rabbit	00126608, 00132172	LD_{50} > 2000 mg/kg	III
81-3	Acute Inhalation - Rat	00126609	LC_{50} > 6.9 m/L	IV
81-4	Primary Eye Irritation - Rabbit	00126608 00132172	Mild Irritant	III

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-5	Primary Skin Irritation - Rabbit	00126608 00132172	Mild Irritant Draize score 0.67/24 hr exposure Draize score 0.19/4 hr exposure	IV
81-6	Dermal Sensitization - Guinea pig	00154270 00154268	Slight Sensitizer	N/A
81-7	Acute Neurotoxicity - Hen	43151201	NOAEL = 500 mg/kg LOAEL = 5,000 mg/kg	N/A
81-8	Acute Neurotoxicity - Rat	43132301	NOAEL = 100 mg/kg LOAEL = 300 mg/kg	N/A

Table 2 summarizes the subchronic and chronic toxicity profile of sulfosate technical. Sulfosate is a neurotoxic chemical which produces clinical findings such as salivation, tremors, emesis, and decreased motor activity in dogs and/or rats. Salivation was the most consistent sign, and in dogs may have served as a precursor to more severe symptoms. In one subchronic study, salivation stopped upon withdrawal of sulfosate and recurred upon reintroduction of treatment. Dogs appear to be the most sensitive species for these effects, with high intra-individual variability in sensitivity.

Table 2. Subchronic and Chronic Toxicity Profile of Sulfosate Technical

Study Type	MRID No.	Results
21-Day Dermal Toxicity-Rabbit	4083702	NOAEL (systemic) = 1,000 mg/kg/day (HTD) LOAEL = Not established
21-Day Dermal Toxicity-Rat (formulation)	41209904	NOAEL (systemic) = 250 mg/kg/day LOAEL (systemic-neurotoxicity) = 1,000 mg/kg/day
Subchronic-Feeding-Mouse	none	Incorporated into the two year mouse oncogenicity study
Subchronic 13 Week-Feeding-Rat	41209902	NOAEL (systemic) = 36 mg/kg/day [800 ppm] LOAEL (systemic) = 88 mg/kg/day [2,000 ppm]
Subchronic 13 Week-Feeding Dog (gavage)	41209903	NOAEL (systemic) = 10 mg/kg/day LOAEL (systemic-neurotoxicity) = 50 mg/kg/day [HDT]
Subchronic 13 Week-Feeding Dog (capsule)	44246704	NOAEL (systemic) = 25 mg/kg/day LOAEL (systemic-neurotoxicity) = 50 mg/kg/day [HDT]
Subchronic Neurotoxicity Screening Battery - Rat	43151202	NOAEL (systemic) = 47.6/54.4 mg/kg/day [600 ppm] LOAEL (systemic-neurotoxicity) = 153.2/171 mg/kg/day [2,000 ppm]

Study Type	MRID No.	Results
Chronic Feeding- One Year Dog	40214005 41325902	NOAEL (systemic) = 10 mg/kg/day LOAEL (systemic-neurotoxicity) = 50 mg/kg/day [HDT]
Chronic toxicity/Carcinogenicity-Rat	40214007 41209905 41209907	NOAEL (systemic) = ≥41.8/55.7 mg/kg/day [≥1,000 ppm] LOAEL (systemic) =≥41.8/55.7 mg/kg/day [≥1,000 ppm] **No evidence of carcinogenicity.**
Carcinogenicity-Mouse	40214006 41209907	NOAEL (systemic) = 118/159 mg/kg/day [1,000 ppm] LOAEL (systemic) = 991/1,340mg/kg/day [8,000 ppm] **No evidence of carcinogenicity**
Developmental Toxicity-Rat	00132183	Maternal NOAEL = 100 mg/kg/day LOAEL = 333 mg/kg/day Developmental NOAEL = 100 mg/kg/day LOAEL = 333 mg/kg/day
Developmental Toxicity-Rabbit	00155526	Maternal NOAEL = 40 mg/kg/day LOAEL = 100 mg/kg/day Developmental NOAEL= 40 mg/kg/day LOAEL = 100 mg/kg/day
Reproductive Toxicity	00154273	Parental/Systemic NOAEL = 6/8 mg/kg/day [150 ppm] LOAEL = 35/41 mg/kg/day [800 ppm] Offspring NOAEL = 6/8 mg/kg/day [150 ppm] LOAEL = 35/41 mg/kg/day [800 ppm]
Metabolism - Rat	00154271	Radiolabelled trimethylsulfonium ion rapidly excreted unmetabolized in urine and feces; principal sites of localization of ion are adrenals, kidneys, bladder, liver, thyroid and stomach.

Study Type	MRID No.	Results
Metabolism - Rat	41235903	IV or oral C14 sulfosate was rapidly excreted: over a 5 day period most (86-95%) of the administered dose was excreted in the urine & feces. IV treated male & females eliminated 90% of the administered dose in urine. Absorption of C14-sulfosate was incomplete by the oral route: Most groups eliminates 47-57% of the administered dose in the urine and 36-42% in the feces. Females treated with a high dose eliminated less in the urine (36% of dose) and more in the feces (54% of dose). Negligible 14CO2 elimination. Tissue C14 residues were < 0.32% of administered dose. Carcass C14 residues were < 2.2% of administered dose (mostly in bones, 3-7 ppm in low dose rats & 19-32 ppm in high dose rats). Most excreted radioactivity (77-96% of fecal; 80-95% of urinary) was unchanged anion (carboxymethylamino-methylphosphonate). One fecal metabolite (repeated dose females; 8.5% of fecal radioactivity) was aminomethyl phosphonic acid. Several minor unidentified (<= 3% total urinary/fecal radioactivity) metabolites were recovered. Low dose = 25 mg/kg. High dose = 250 mg/kg (toxic signs were lethargy, moderate to severe depression, tremors, dehydration, decreased food consumption in 2 - 5 rats (total = 10). Recovery within 72 hours.

LOAEL = lowest observed adverse effect level; NOAEL = no observed adverse effect level

In an acute neurotoxicity study (MRID 43132301), sulfosate technical (purity 59.4%) was used to treat rats (10/sex/dose) by gavage with doses of 0, 30, 100 or 300 mg/kg. Acute neurotoxicity effects observed after a single dose of 300 mg/kg (LOAEL) in the rat included ptosis, decreased activity, decreased splay reflex, upward curvature of spine, shaking, sides pinched in, signs of urinary incontinence, irregular breathing, hunched posture, abnormal or staggering gait, increased time to tail flick, decreased landing foot splay, decreased forelimb grip strength, decreased hindlimb grip strength, and decreased motor activity. There was also death at this dose. There was no microscopic evidence of neurotoxicity. The NOAEL was 100 mg/kg.

Technical glyphosate trimesium (sulfosate, 59.4%) was tested in a 90-day neurotoxicity feeding study (MRID 43151202) in Alpk:APfSD rats. The animals (12/sex/group) received either 0, 200, 600, or 2,000 ppm (0, 15.6, 47.6 or 153.2 mg/kg/day for males; 0, 18.2, 54.4 or 171.0 mg/kg/day for females) in the diet. At 2,000 ppm (LOAEL), decreased body weights (16% for males and 9% for females), food consumption and utilization were observed. In addition, mean forelimb grip strength values for high dose females were statistically significantly decreased over the control values during weeks 5-14 (75 - 82% of controls). There was no microscopic evidence of neurotoxicity. The significance of the decreased grip strength as a neurotoxicological effect is less certain since there were no effects in mean hindlimb grip strength for high dose females, in either of the mean grip strength values at any time period for males, in any of the other functional

battery parameters, in motor activity values or in neuropathology microscopic examinations for either sex. However, it occurred at all time points, was statistically significant, and signs of neurotoxicity occur in other studies. The NOAEL was 600 ppm (47.6 mg/kg/day).

Male and female beagle dogs were given sulfosate (ranging from 19.2% a.i. to 59.4% a.i.) in feed for a period of either 90 days (gavage (MRID 41209903) and capsule (MRID 44246704)) or one year (MRID 40214005, 41235902) at doses ranging from 2 to 50 mg/kg/day. In both subchronic and chronic studies the LOAEL (50 mg/kg/day) was based on clinical signs of neurotoxicity (salivation and/or emesis). Hydrocephalus or dilated ventricles were observed in at least one animal at the highest dose tested (HDT) (50 mg/kg/day) in adult dogs following both 90-days (gavage or capsule) and one year of dosing. This finding was never seen in controls or low dose groups. Hydrocephaly and/or dilated ventricles in dogs of this age may have been due to inherent asymptomatic incidences in the beagle (Vullo et al., 1997[1]), but it was noted that these animals were not supplied by the same breeding colony, and the incidences were only observed at the high dose levels across several studies. Therefore, these findings could not be dismissed.

In a 21-day dermal study (MRID 41209904), 4 LC-E formulation (39.8% sulfosate) was applied to the skin of Alpk:AP (Wistar derived) rats (5/sex/group) at doses of 0, 25, 250, or 1,000 mg/kg. Neuropathology (sciatic nerve degeneration) was observed at 1,000 mg/kg (LOAEL). The NOAEL was 250 mg/kg/day. In a 21 day dermal study (MRID 4083702), rabbits (New Zealand White) were treated with sulfosate (SC-0224 Concentrate (51.2% a.i.)) at doses of 0, 10, 100, and 1,000 mg/kg/day, 6 hrs/day, 5 days/wk for 3 weeks. There was no systemic toxicity at any dose. Mild erythema at application sites was seen in all sulfosate-treated groups. The systemic NOAEL is 1,000 mg/kg/day (limit dose).

In a carcinogenicity feeding study (MRID 40214006, 41209907), Crl:CD-1(ICR)BR mice (60/sex/dose) were given sulfosate technical (56.17% pure) in the diet at concentrations of 0 (dietary control), 0 (vehicle control), 100, 1,000 and 8,000 ppm (males - 0, 0, 11.7, 118, or 991 mg/kg/day; females - 0, 0, 16.0, 159, or 1341 mg/kg/day) for 2 years. Degeneration of the sciatic nerve, lumbar spinal root, and lumbar spinal white matter in males was seen at 991 mg/kg. Although these findings lack supporting neuropathology data in the acute and subchronic neurotoxicity studies in rats, the overall neurotoxicity profile of the chemical indicated that the neuropathology could be a treatment-related effect of concern.

Based on the available mutagenicity studies, there are no concerns for mutagenicity at this time (Table 3). In some of the *in vitro* mutagenicity tests (forward mutation/mouse lymphoma cells, structural chromosomal aberrations/CHO cells) conducted in 1982, sulfosate induced a false positive mutagenic effect. A common feature of these tests was that the pHs of the test incubation media were acidic (pH 5.67-7.07) due to the addition of sulfosate. These positive

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[1]**Reference**: Vullo, T., E. Korenman, R.P. Mazo, D.G. Gonez, M.D. Deck, and P.T. Cahill. 1997. Diagnosis of cerebral ventriculomegaly in normal adult beagles using quantitative MRI. *Vet. Radiol. Ultrasound*, Jul.-Aug. 38 (4):277-81.

results were no longer observed when the pH was readjusted to a more physiological level (pH 7.4) before the mutagenicity tests were conducted.

Table 3 - Mutagenicity Data Base

STUDY TYPE REFERENCE	CONCLUSIONS
Gene Mutation/bacteria - Ames *Salmonella typhimurium* (MRID # 00126612)	**Sulfosate** (SC-0224 lot #7269-10 and lot #7646-0901 19.2% pure by weight (90% a.i.)) **Not mutagenic** in TA1535, TA1537, TA1538, TA98, and TA100 Tested with and without metabolic activation. Doses tested: 0.12,0.37, 1.11,3.33, and 10 mg/plate without S9 metabolic activation; 0.56,1.11, 1.67,3.33,5.0,10.0, and 15.0 mg/plate with S9 metabolic activation. Acceptable
Gene Mutation/bacteria - Ames *Salmonella typhimurium* (MRID # 00155527)	**Sulfosate** (SC-0224, 55.6% pure, lot # JHC 8865-20-1). **Not a mutagen** up to 40 ul/plate with TA1535, TA1537, TA98, and TA100 strains of Salmonella typhimurium in either the standard plate assay or the preincubation assay with and without the metabolic activation. Concentrations tested: 2.5, 5.0, 10.0, 20.0, and 40.0 ul/plate. Acceptable
Gene Mutation/*In vitro* assay in Mammalian cells Mouse Lymphoma (MRID # 00126616)	**Sulfosate** -- Mouse - L5178Y ($TK^{+/-}$) (SC-0224 90% & 58.5% ai, lots 7269-10 & 6841-48-3 6841-48-4) **Positive mutagenicity** observed at the thymidine locus under S-9 rat liver metabolic activation. Dose levels tested: 0.375, 0.75, 1.50, 3.0, 6.0, 8.0, 8.5, 9.0, 9.5 and 10 mg/ml in the absence and presence of S-9 metabolic activation. Acceptable
Gene Mutation/*In vitro* assay in Mammalian cells Lymphoma Mutation (MRID # 00155528)	**Sulfosate** -- Mouse - L5178Y ($TK^{+/-}$) (SC-0224, 55.6% pure, lot # JHC 8865-20-1) - Species: Mouse) **Mutagenic** effect was observed under the standard test procedure **with and without the metabolic activation** at the concentrations tested (3.5 through 5.0 µl/ml). Concentrations tested: 1 through 5.4 µl/ml under the nonactivation assay system; 2.5 through 5.0 µl/ml under the activation assay system. Acceptable
Gene Mutation/*In vitro* assay in Mammalian cells Lymphoma Mutation (MRID # 00155528)	**Sulfosate** (SC-0224)-- Species: Mouse Mutagenic in this assay with and without metabolic activation under the pH unadjusted test condition (pH 5.62-7.07) - through 5 ug/ml. 3/30/97 Addendum: Not a mutagen in this assay with and without metabolic activation under the pH adjusted test condition (pH 7.4) 5 through 10 ul/ml conc. Used. L51781 mouse cells. Acceptable
Cytogenetics Sex Link Recessive - Drosophila melanoga (MRID 00126610)	**Sulfosate** (SC-0224) - Species: Drosophila melanoga. **Not mutagenic** in SLRL test. Doses tested: 25 and 50 mg/ml. Acceptable

STUDY TYPE REFERENCE	CONCLUSIONS
Cytogenetics - *in vitro* -mouse (MRID 00155529) a) Chromosomal Aberration b) SCE)	**Sulfosate** - (SC-0224, 55.6% pure, lot # JHC 8865-20-1) L51781 mouse cells (A) Chromosomal Aberration Assay Under the standard test procedure **positive clastogenic effect** was observed at the concentration of 5 ul/ml under the nonactivation assay and at the concentrations of 3 to 5 ul/ml under the activation assay. Concentrations tested: 1 through 5 ul/ml under the nonactivation assay; 3 through 5 ul/ml under the activation assay. (B) Sister Chromatid Exchange Assay Under the standard test procedure, the test compound **was a positive inducer of SCE** at the concentration of 5 ul/ml under the nonactivation assay and at the concentrations of 3 to 5 ul/ml under the activation assay. Concentrations tested: 1 through 5 ul/ml under the nonactivation assay; 3 through 5 ul/ml under the activation assay. Acceptable
Cytogenetics *In vitro* mouse (MRID 00155529)	Clastogenic in these assays with and without metabolic activation under the pH unadjusted test condition (PH5-62-7.07)-3 through 5 ul/ml. 3/20/87 Addendum: **Not a clastogen** in these assays with & without metabolic activation under the **pH adjusted** test condition (PH 7.4)-4 through 10 ul/ml. L51781 mouse cells. Acceptable
Cytogenetics *In vitro* CHO (MRID 00155530) a) Chromosomal Aberration b) SCE)	**Sulfosate** -(SC-0224) CHO (A) Chromosomal Aberration Assay. **Not a clastogen** up to 10 ul/ml under the adjusted acidic test condition with and without the metabolic activation system. Concentrations tested: 4 through 10 ul/ml under the nonactivation or the activation system. (B) Sister Chromatid Exchange Assay; **Not an inducer up to 10 ul/ml** under the adjusted acidic test condition with and without the metabolic activation system. Concentrations tested: 4 through 10 ul/ml under the nonactivation or the activation system. **Unacceptable**
Cytogenetics *In vitro* CHO (MRID 00126614)	**Sulfosate** - Hamster (Chinese) (SC-0224 ,58.5% ai, lot #684 1-48-3) Sister chromatid exchange not determined. **Positive for the induction of chromosomal aberration** in CHO cells in the absence (4 mg/ml) and presence (8,10,12 mg/ml) of S9 metabolic activation. Doses tested: 2,4, and 6 mg/ml in the absence of S9 metabolic activation; 2,4,6,8,10, & 12 mg/ml in the presence of S9 metabolic activation. Acceptable
Cytogenetics *In vitro* CHO (MRID 00126615)	**Sulfosate** (SC-0224, 72% ai, lot #7466-18-01)- Hamster (Chinese) **Increased chromosomal aberrations in activation assay** at 6 - 8 ul/ ml. **No increase in sister chromatid exchanges with S-9 metabolic activation,** (1 through 8 ul/ml). Dose tested: 2,4,6,8,10 and 12 ug/ml with S9 metabolic activation; 2,4, and 6 ul/ml without S9 metabolic activ. Acceptable
Cytogenetics *In vitro* CHO (MRID 00155530)	**Sulfosate** (SC-0224)- Hamster (Chinese) 3/20/87 Addendum. **Not a clastogen** in these assays with and without metabolic activation under the pH adjusted test condition (pH 7.4 to 7.6). Concentrations tested: 4 through 10 ul/ml. Acceptable

STUDY TYPE REFERENCE	CONCLUSIONS
Cytogenetics *In vivo* mouse micronucleus assay (MRID #40214004, 41209908)	**Sulfosate** - Mouse (Charles River CD-1) (SC-0224, EHC0701-25;lot # JHC8865-20-1, 55.3% pure) **Failed to induce significant increase in the number of PCE** containing micronuclei. Dose levels tested: 700, 900, & 1100 mg/kg for males & 400, 600, & 800 mg/kg for females. Acceptable
Cytogenetics Rat Bone Marrow (MRID 00126611)	**Sulfosate** (SC-0224 58.5% ai) - Rat Bone Marrow **Not clastogenic** in the rat bone marrow cells. Doses tested: 21, 63, and 188 mg/kg. Acceptable
Other (MRID 00126616)	**Sulfosate** - BALB/3T cells transformation assay. (SC-0224, est. 90% tech, lot #7269-10) **Negative** responses at 0.313, 0.625, 1.25,2.50, and 5.0 mg/ml in the BALB/3T cells transformation assay. Acceptable

Based on the lack of evidence of carcinogenicity in mice (MRID 40214006, 41209907) and rats (MRID 40214007, 41209905, 41209907) at doses that were judged to be adequate to assess the carcinogenic potential, sulfosate was classified as a **"Group E"** chemical - no evidence for carcinogenicity in humans - based on the *"Guidelines for Carcinogen Risk Assessment" [FR51: 33992-34003, 1986]* for classifying the weight-of-evidence for carcinogenicity. (RfD report - 26-JUL-1994).

The available developmental toxicity data provided no indication of increased susceptibility in rats or rabbits from *in utero* and/or post natal exposure to sulfosate. In the prenatal developmental toxicity study in rats, evidence of developmental toxicity was seen only in the presence of maternal toxicity. In the developmental toxicity study in rabbits, developmental toxicity was seen in the presence of maternal toxicity at the highest dose level. In the two-generation reproduction study in rats, effects in the offspring were observed only at or above treatment levels which resulted in parental toxicity.

In the rat developmental toxicity study (MRID 00132183), animals (25/dose) were treated with sulfosate (19.2% a.i.) by gavage on gestation days 6-20 at dose levels of 0, 30, 100, or 333 mg/kg/day. The maternal LOAEL was 333 mg/kg/day based on decreased body weight, feed consumption and body weight gain along with increased incidences of salivation, chromorhinorrhea, and lethargy after dosing. The maternal NOAEL was 100 mg/kg/day. The developmental toxicity LOAEL was 333 mg/kg/day based on decreased fetal body weight. The developmental toxicity NOAEL was 100 mg/kg/day.

In the rabbit developmental toxicity study (MRID 00155526), animals (15/group except 21 at the high dose) were treated by gavage with sulfosate (56.2% a.i.) on gestation days 7-19 at dose levels of 0, 10, 40 or 100 mg/kg/day. The maternal LOAEL was 100 mg/kg/day (6 deaths in 17 pregnant does, 4 abortions in the 11 survivors along with decreased body weight, feed

consumption and body weight gain). The maternal NOAEL was 40 mg/kg/day. The developmental LOAEL was 100 mg/kg/day based on decreased number of live fetuses/doe for 7 surviving rabbits (5.4 versus 7.4 in controls), 4 rabbits aborted their litters. Having only 7 litters does not give a sufficiently high number of animals to absolutely conclude that no developmental toxicity is occurring, particularly in light of the massive losses to death and abortions. The developmental NOAEL is 40 mg/kg/day.

In the two-generation reproduction study (MRID 00154273), Sprague-Dawley rats (20 male and 30 female/group) received sulfosate (19.2% a.i.) at dose levels of 0, 150, 800, or 2,000 ppm in the diet (average for P0 and P1 - males - 0, 6, 35, 88.5 mg/kg/day; females - 0, 8, 41, 98 mg/kg/day). The systemic LOAEL was 800 ppm (35/41 mg/kg/day for males/females) based on a decrease in absolute and sometimes relative organ weights in both generations (thymus, heart, kidney and liver) at 800 and 2000 ppm and a decrease in body weights and body weight gains during the premating period at 2000 ppm. The systemic NOAEL was 150 ppm (6/8 mg/kg/day for males/females, respectively). The reproductive/developmental LOAEL was 800 ppm (35/41 mg/kg/day for males/females, respectively) based on decreased litter size in F0a and F1b litters at 2,000 ppm and on decrease in mean pup weights during lactation in second litters at 800 ppm and in all litters at 2,000 ppm. The reproductive/developmental NOAEL was 150 ppm (6/8 mg/kg/day for males/females, respectively).

There are no dermal absorption studies available for review. A dermal absorption factor is not required since no toxicological endpoints were identified for dermal risk assessments at this time.

Overall, the quality of the toxicological database is good and confidence in the hazard data and dose response assessment is high. There are no data gaps for the standard Subdivision F Guideline requirements for a food-use chemical by 40 CFR Part 158, however, a developmental neurotoxicity study in the rat is required. This is based on the weight-of-the-evidence for concerns of neurotoxicity in the mouse oncogenicity study, subchronic and chronic dog studies, 21-day dermal toxicity study in rats, and acute and subchronic neurotoxicity studies in the rat (Memo, M. Copley and J. Rowland, HED Doc. No. 012652, 6/25/98).

3.2 FQPA Considerations

On June 12, 1998, HIARC met to re-examine the neurotoxicity hazard assessment/characterization for sulfosate. This was a follow-up to the HIARC meeting held on April 26, 1998, which met to re-assess the RfD established in 1994 and select the toxicological endpoints for acute dietary as well as occupational exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to sulfosate as required by the Food Quality Protection Act (FQPA) of 1996. The HIARC determined that a developmental neurotoxicity study in rats is required to characterize the observed neuropathology in the subchronic and chronic studies (Memo, M. Copley and J. Rowland, HED Doc. No. 012652, 6/25/98). The FQPA SFC met on June 29, 1998 to re-evaluate the hazard and exposure data for sulfosate and recommended application of a 3x Safety Factor to ensure

protection of infants and children (Memo, B. Tarplee and J. Rowland, HED DOC. No. 01268, 6/29/98). The reports of the HIARC (6/25/98) and the FQPA Safety Factor Committee (6/29/98) are included as Attachments 1 and 2, respectively.

3.2.1. Special Sensitivity to Infants and Children

1. Adequacy of the Database:

   Acceptable hen delayed neurotoxicity and acute and subchronic rat neurotoxicity screening studies have been submitted to the Agency. Acceptable prenatal toxicity studies in rats and rabbits and a 2-generation reproductive toxicity study in rats on sulfosate have been submitted to the Agency. However, a developmental neurotoxicity is required based on the neurotoxicity observed in dogs, rats and mice (see below).

2. Neurotoxicity:

   Sulfosate has shown evidence of neurotoxicity in several studies in rats, dogs and mice.

   Rats: In an acute neurotoxicity study in rats (MRID 43132301), neurotoxic effects observed after a single dose of 300 mg/kg (LOAEL) included ptosis, decreased activity, decreased splay reflex, upward curvature of spine, shaking, sides pinched in, signs of urinary incontinence, irregular breathing, hunched posture, abnormal or staggering gait, increased time to tail flick, decreased landing foot splay, decreased forelimb grip strength, decreased hindlimb grip strength, and decreased motor activity. There was also death at this dose. There was no microscopic evidence of neurotoxicity. In a 90-day neurotoxicity feeding study (MRID 43151202) in rats, there was a decrease in mean forelimb grip strength at 171 mg/kg/day. There was no microscopic evidence of neurotoxicity. The significance of the decreased grip strength as a neurotoxicological effect is less certain since there were no effects in mean hindlimb grip strength for high dose females in either of the mean grip strength values at any time period for males, in any of the other functional battery parameters, in motor activity values, or in neuropathology microscopic examinations for either sex. However, it occurred at all time points, was statistically significant, and signs of neurotoxicity occur in other studies. In a developmental toxicity study in rats (MRID 00126618, 00132183, 00155387), clinical signs of neurotoxicity included salivation, lethargy, and chromorhinorrhea at 333 mg/kg/day. In a 21-day dermal study (MRID 41209904) in rats, neuropathology (sciatic nerve degeneration) was observed at 1,000 mg/kg (LOAEL).

   Dogs: In both subchronic (gavage (MRID 41209903) and capsule (MRID 44246704)) and chronic (MRID 40214005, 41235902) studies in beagle dogs, the LOAEL (50 mg/kg/day) was based on clinical signs of neurotoxicity (salivation and/or emesis). Hydrocephalus or dilated ventricles were observed in at least one animal at the highest dose tested (HDT) (50 mg/kg/day) in adult dogs following both 90-days (gavage or

capsule) and one year of dosing. This finding was never seen in controls or low dose groups. Hydrocephaly and/or dilated ventricles in dogs of this age may have been due to inherent asymptomatic incidences in the beagle (Vullo et al., 1997[2]), but it was noted that these animals were not supplied by the same breeding colony, and the incidences were only observed at the high dose levels across several studies. Therefore, HIARC agreed that these findings could not be dismissed. In a 28-day gavage study (summary only available), clinical signs (decreased activity, emesis, salivation, tremors and/or shaking) were seen at 36 mg/kg/day.

Mice: In a 2-year oncogenicity study in mice (MRID 40214006), degeneration of the sciatic nerve, lumbar spinal root, and lumbar spinal white matter in males was seen at 991 mg/kg. Although these findings lack supporting neuropathology data in the acute and subchronic neurotoxicity studies in rats, the overall neurotoxicity profile of the chemical indicated that the neuropathology could be a treatment-related effect of concern.

Based upon a weight-of-evidence consideration of neurotoxicity noted above, HIARC decided to require the conduct of a developmental neurotoxicity study with sulfosate to evaluate the potential for effects on functional development (Memo, M. Copley and J. Rowland, HED Doc. 012652, 6/25/98). [Note: Also considered in the weight-of-evidence were: 1) No evidence of treatment-related anomalies in the development of the fetal nervous system were observed in the prenatal developmental toxicity studies in either rats or rabbits at maternally toxic oral doses up to 333 or 100 mg/kg/day, respectively; 2) No clinical observations indicative of neurobehavioral or functional abnormalities were reported in the two-generation reproduction study in rats; 3) No effects on brain weight were observed in any of the guideline studies in which these parameters were measured; 4) No evidence of cholinesterase inhibition was observed for sulfosate; 5) Sulfosate is not a potent toxicant; it has an oral LD_{50} of 748 mg/kg in rats; and 6) SAR: Glyphosate, a related chemical, is not neurotoxic.]

- Developmental/Reproductive Toxicity:

Developmental Toxicity: In a prenatal developmental toxicity study, sulfosate was administered by gavage to groups of pregnant Sprague-Dawley rats on gestation days 6-20 at dose levels of 0, 30, 100, or 333 mg/kg/day. The maternal NOAEL was 100 mg/kg/day and LOAEL was 333 mg/kg/day based on decreased body weight, food consumption, and increased clinical signs. The developmental NOAEL was 100 mg/kg/day and LOAEL was 333 mg/kg/day based on decreased fetal body weight. (MRID 00132183)

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[2]**Reference**: Vullo, T., E. Korenman, R.P. Mazo, D.G. Gonez, M.D. Deck, and P.T. Cahill. 1997. Diagnosis of cerebral ventriculomegaly in normal adult beagles using quantitative MRI. *Vet. Radiol. Ultrasound*, Jul.-Aug. 38 (4):277-81.

In a prenatal developmental toxicity study, sulfosate was administered by gavage to groups of New Zealand White rabbits on gestation days 6-18 at doses of 0, 10, 40, or 100 mg/kg/day. The maternal NOAEL was 40 mg/kg/day and LOAEL was 100 mg/kg/day based on abortions, deaths, decreased body weight and food consumption. The developmental NOAEL was 40 mg/kg/day and LOAEL was 100 mg/kg/day based on decreased number (7) of surviving does, and decrease in number of live fetuses/doe (5.4 vs 7.4 in controls). (MRID 00155526)

Reproductive Toxicity: Sulfosate was administered by diet to Sprague-Dawley rats at dose levels of 0, 150, 800, or 2000 ppm for two generations. The parental systemic NOAEL was 140 ppm (7.5 mg/kg/day) and the LOAEL was 800 ppm (40 mg/kg/day) based on decreased body weight, decreased organ weights and decreased food consumption. The reproductive/offspring NOAEL was 7.5 mg/kg/day (140 ppm) and LOAEL was 40 mg/kg/day (800 ppm) based on decreased pup body weight during lactation. (MRID 00154273)

Determination of Susceptibility: The data provided no indication of increased susceptibility in rats or rabbits from *in utero* and/or post natal exposure to sulfosate. In the prenatal developmental toxicity study in rats, evidence of developmental toxicity was seen only in the presence of maternal toxicity. In the developmental toxicity study in rabbits, developmental toxicity was seen in the presence of maternal toxicity at the highest dose level. In the two-generation reproduction study in rats, effects in the offspring were observed only at or above treatment levels which resulted in parental toxicity.

3.2.2 Determination of the FQPA Safety Factor:

The FQPA SFC (29-June-1998) recommended that the 10x factor for increased susceptibility of infants and children (as required by FQPA) should be **reduced to 3x**.

The FQPA SFC determined that the data indicate that there is no increased susceptibility to young rats or rabbits following *in utero* exposure in prenatal studies or in the postnatal study in rats, and the guideline requirements for the toxicology data base are complete. However, the FQPA SFC recommended that the FQPA Safety Factor should not be removed, instead it should be reduced to 3x because of the concern for the overall neurotoxicity exhibited in long-term studies in adult animals (mice, rats, and dogs). In mice, sulfosate induced degeneration of the sciatic nerve, lumbar spinal root and lumbar spinal white matter was reported. In rats, degeneration of the sciatic nerve was seen following dermal applications. In dogs, hydrocephalus and/or dilated ventricles were observed following subchronic and chronic exposures. In addition, clinical signs indicative of neurotoxicity such as salivation, tremors, emesis, decreased activity was seen in rats and dogs. Based on these factors, the HIARC determined that a developmental neurotoxicity study is required to characterize the observed neuropathology in the subchronic and

chronic studies. The FQPA SFC concurred with the HIARC and thus determined the need for a 3x safety factor.

The Committee determined that the **FQPA Safety Factor (3x)** is applicable for the following subpopulations:

> Acute Dietary: All populations which include Infants and Children. The endpoint is based on mortality, decreased body weight and food consumption, and neurotoxicity observed after a single dose in the Acute Neurotoxicity Study in Rats.
>
> Chronic Dietary: All populations which include Infants and Children. The endpoint is based on clinical signs indicative of neurotoxicity (emesis and salivation) in the One-Year Chronic Dog study.

3.3 Other FQPA Considerations

3.3.1. Cumulative Risk

Sulfosate is structurally similar to glyphosate. Other pesticides may have common toxicity endpoints with sulfosate. However, EPA does not have data available at this time to determine whether sulfosate has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of this tolerance action, therefore, EPA has not assumed that sulfosate has a common mechanism of toxicity with other substances.

On this basis, the petitioner must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether sulfosate shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for sulfosate need to be modified or revoked.

3.3.2. Endocrine Disruption

EPA is required to develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect...". The Agency is currently working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed 3 years from the passage of FQPA (August 3, 1999) to implement this program. At that time, EPA may require further testing of sulfosate for endocrine disrupter effects.

3.4 Dose Response Assessment

The doses and toxicological endpoints selected for various exposure scenarios are summarized in Table 4. No residential uses exist for this chemical.

Dietary Exposures

The **acute RfD** (aRfD) of 1.0 mg/kg was based on an acute neurotoxicity study in the rat (MRID 43132301). The NOAEL was 100 mg/kg, based on mortality, decreased body weight and food consumption, and neurotoxicity at the LOAEL of 300 mg/kg. An uncertainty Factor (UF) of 100 was applied to account for both inter-species extrapolation (10) and intra-species variations (10).

The **chronic RfD** (cRfD) of 0.10 mg/kg/day was based on a one year feeding study in dogs (MRID 40214005, 41235902). The NOAEL was 10 mg/kg/day, based on emesis and salivation at the LOAEL of 50 mg/kg/day (HDT). The LOAEL is supported by subchronic dog studies where salivation and emesis occurred at 50 mg/kg/day in a 90-day study and at 75 mg/kg/day in a 28 day study; with death occurring within 3 days at 150 mg/kg/day in the 28 day study. An UF of 100 was applied to account for both interspecies extrapolation (10) and intra-species variations (10). The HIARC concurred with the RfD established in 1994.

Based on the lack of evidence of carcinogenicity in mice (MRID 40214006, 41209907) and rats (MRID 40214007, 41209905, 41209907) at doses that were judged to be adequate to assess the carcinogenic potential, sulfosate was classified as a **"Group E"** chemical - no evidence for carcinogenicity in humans - based on the *"Guidelines for Carcinogen Risk Assessment" [FR51: 33992-34003, 1986]* for classifying the weight-of-evidence for carcinogenicity (Memo, G. Ghali, RfD/Peer Review Report, HED Doc. No. 011156, 7/26/94). Therefore, a chronic cancer dietary risk assessment is not required.

Recommendation for Aggregate Exposure Risk Assessments

There are no registered or proposed residential uses at the present time. Therefore, aggregate exposure risk assessments will be limited to food + water.

TABLE 4 - Summary Of Toxicology Endpoints For Risk Assessment

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOAEL = 100 mg/kg/day	Clinical signs indicative of neurotoxicity (tail flick, landing foot splay, forelimb grip strength, hindlimb grip strength and motor activity), decreased body weight and food consumption, and mortality.	Acute Neurotoxicity-Rat

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
	UF = 100 FQPA SF = 3	**Acute RfD = 1.0 mg/kg** **Acute PAD[a] = 0.333 mg/kg/day**	
Chronic Dietary	NOAEL = 10 mg/kg/day	Clinical signs indicative of neurotoxicity (emesis and salivation).	Chronic Toxicity - Dog
	UF = 100 FQPA SF = 3	**Chronic RfD = 0.10 mg/kg/day** **Chronic PAD[a] = 0.0333 mg/kg/day**	

[a]PAD = Population Adjusted Dose = $\frac{\text{Acute or Chronic RfD}}{\text{FQPA Safety Factor}}$

4.0 EXPOSURE ASSESSMENT

4.1 Summary of Registered Uses

Amended labels have been proposed for use of sulfosate formulated as Touchdown®, 6 lb/gal SC formulation, EPA Reg. No. 10182-324, and Touchdown® BTU, 5 lb/gal SC formulation, EPA Reg. No. 10182-429 to add a preharvest use and to add uses on glyphosate-tolerant soybeans. The proposed label recommends multiple broadcast applications before, during, or after planting prior to crop emergence on minimum or no-till planted soybeans at 0.4-4 lb ai/A/application. Sulfosate formulations can also be applied as a spot spray (to weeds) and by wiper or wick. A preharvest application may be made at 1 lb ai/A as a harvest aid. The maximum yearly application, no matter which treatments are made, is 8 lb ai/A. A 7-day PHI is proposed following preharvest applications and wiper or wick applications. An 8-week PHI is proposed following spot applications. The grazing or harvesting for hay following harvest aid application is prohibited.

Sulfosate may also be applied preemergence, postemergence, and preharvest as multiple broadcast applications to soybean varieties that have been genetically modified to be tolerant to glyphosate herbicides. Preemergence applications may be made at 0.4-4 lb ai/A/application, postemergence applications may be made at 2 lb ai/A/application, and preharvest applications may be made at 1 lb ai/A/application. The maximum yearly application, no matter which treatments are made, is 8 lb ai/A. A 7-day PHI is proposed following preharvest applications. Postemergence applications may be made up to and including the full bloom stage of soybeans. The grazing or harvesting of glyphosate-tolerant soybeans for feed is prohibited.

Broadcast applications may be made in 10-30 gal/A with conventional ground equipment or in 3-10 gal/A with low-volume ground equipment; applications may be made using aerial equipment in a minimum of 3 gal/A. The use of a surfactant or wetting agent is

required. Sulfosate formulations may be tank mixed with other herbicides registered for these uses.

4.2 Dietary Exposure

4.2.1 Food Exposure

Residue chemistry data submitted with this petition has been reviewed in a separate document (Memo, G. Kramer, 4/23/99; DP Barcode D243318).

4.2.1a Nature of the Residue

Plants and Animals (OPPTS GLN 860.1300): Sulfosate metabolism studies in plants have been submitted in conjunction with previous petitions. The nature of the residue is considered to be understood in corn, grapes, and soybeans. The Agency concluded that the parent ions are the residues of regulatory concern for sulfosate in these crops.

The submitted metabolism studies are adequate to delineate the metabolism of PMG and TMS in the seed of glyphosate-tolerant soybeans. The total radioactive residue (TRR) in soybean seed treated with three applications of [^{14}C]PMG-TMS at 1x the maximum proposed application rate was 10.0 ppm. PMG was identified at 26% TRR (2.6 ppm) and the metabolite AMPA (aminomethylphosphonic acid) was identified at 38% TRR (3.8 ppm). An additional 7% TRR was found to be associated with triglycerides and monosaccharides (radioactivity was observed in monosaccharides following hydrolysis of nonextractable residues). These results are similar to the previously submitted soybean metabolism study with [^{14}C]PMG-TMS in which PMG and AMPA were the only metabolites identified. In the previous study, PMG and AMPA were identified at much lower levels, which is consistent with the difference in use patterns in the two studies.

The TRR in soybean seed treated with three applications of PMG-[^{14}C]TMS at 1x the maximum proposed application rate was 23.0 ppm. TMS was identified at 90% TRR (20.7 ppm). A small amount of radioactivity (1% TRR) was found to be associated with triglycerides. These results are similar to the previously submitted soybean metabolism study with PMG-[^{14}C]TMS in which TMS was found to be the major residue. **HED thus concludes that the parent ions are also the residues of regulatory concern for sulfosate in glyphosate-tolerant soybeans.**

4.2.1b Residue Analytical Method (OPPTS GLN 860.1340)

Plants:

PMG: There is currently a PAM II enforcement method for PMG in crops.

TMS: The registrant has proposed GC Method RR 93-105B as the analytical enforcement method. A successful Petition Method Validation (PMV) of this analytical enforcement method for the TMS moiety in plants has been completed by the EPA laboratory (Memo, G. Kramer 1/23/96; D219447). HED concludes that Method RR 93-105B is adequate for enforcement of the permanent tolerances.

Animals:

PMG: The registrant has proposed GC Method RR 93-104B as the analytical enforcement method. A successful PMV of this analytical enforcement method for the PMG moiety in meat, milk and eggs has been completed by the EPA laboratory (Memo, G. Kramer 5/13/96; D225926). HED concludes that Method RR 93-104B is adequate for enforcement of the permanent tolerances.

TMS: The registrant has proposed GC Method RR 93-100B as the analytical enforcement method. A successful PMV of this analytical enforcement method for the TMS moiety in meat, milk and eggs has been completed by the EPA laboratory (Memo, G. Kramer 1/22/96; D221382). HED concludes that Method RR 93-100B is adequate for enforcement of the permanent tolerances.

4.2.1c Multiresidue Method (OPPTS GLN 860.1360)

A report on the behavior of PMG and TMS (MRID 41209915) in FDA Multiresidue protocols I, II, III, and IV, has been forwarded to the FDA for review.

4.2.1d Storage Stability Data (OPPTS GLN 860.1380)

The petitioner has demonstrated residues of TMS and PMG to be stable in soybean seed, forage and hay for up to 2 years (Memo, S. Koepke 5/9/91); in sorghum grain for up to 4 years (Memo, S. Koepke 12/21/90); in wheat grain for up to 2 years (Memo, S. Koepke 12/21/90); in orange fruit for up to 2 years (Memo, S. Malik 10/10/91); and in grapes for up to 2 years (Memo, B. Schneider 10/30/91). The soybean seed samples from the submitted field trials were analyzed within 6 months of collection; therefore, no additional storage stability data are required to support the submitted field trials on soybean seed.

4.2.1e Meat and Milk, Poultry and Eggs (OPPTS GLN: 860.1480)

No additional feeding studies were submitted with this petition. Based on the proposed tolerances (and proposed tolerances for wheat commodities), the maximum theoretical dietary burdens of sulfosate to beef and dairy cattle are 379 and 396 ppm, respectively. A ruminant feeding study has been submitted previously and reviewed by the Agency (Memo, S. Koepke 4/29/91); the feeding study reflected dosing levels of 50, 300, and

1000 ppm. Based on the results of this study, the proposed tolerances for meat and milk commodities are not appropriate. **A revised Section F, proposing the following meat and milk tolerances, is required:**

Cattle, goat, hog, sheep, and horse kidney	6.0 ppm
Cattle, goat, hog, sheep, and horse meat byproducts (exc. kidney)	1.5 ppm
Cattle, goat, hog, sheep, and horse meat	1.0 ppm
Cattle, goat, hog, sheep, and horse fat	0.5 ppm
Milk	1.5 ppm

No additional poultry tolerances were proposed and no additional poultry feeding studies were submitted with this petition. The maximum theoretical dietary burden of sulfosate to poultry is 9.6 ppm. The petitioner has previously submitted a poultry feeding study (CBTS Nos. 6814, 6815, and 6816, 4/29/91, S. Koepke) reflecting dosing levels of 0.5, 5, and 50 ppm. Based on the results of this study, the existing tolerance for eggs is not adequate. **A revised Section F, proposing the following tolerance is required:**

Eggs	0.05 ppm

4.2.1f Crop Field Trials (OPPTS GLN 860.1500)

A total of 20 soybean field trials were conducted in 1996 in Regions 2 (NC and TN), 4 (AR, LA, and MS), and 5 [IA(3), IL(3), IN(1), KS(1), MN(2), MO(1), NE(1), OH(1), SD(1), and WI(1)]. Mature soybean seed was harvested 6-7 days following the last of three broadcast applications of the 6 lb/gal SC formulation (EPA Reg. No. 10182-324). The first application was made preemergence at 5 lb ai/A/application, followed by a second application made at the R2 growth stage at 2 lb ai/A/application, and the final application was made 6-7 days prior to seed harvest at 1 lb ai/A/application. The total application rate was 8 lb ai/A (1x the maximum proposed seasonal rate). The submitted residue data for soybean seed are adequate. The submitted data indicate that combined residues of PMG and TMS will not exceed the proposed tolerance of 21 ppm (of which no more than 13 ppm is trimethylsulfonium) in/on soybean seed harvested following the maximum proposed application rate. The combined residues of PMG and TMS were 1.78-20.27 ppm (1.16-12.47 ppm of which was TMS) in/on soybean seed harvested 6-7 days following the last of three broadcast applications of the 6 lb/gal SC formulation at a total rate of 8 lb ai/A (1x the maximum proposed seasonal application rate). The average residue in soybean seed was 6.7 ppm.

The requirements for soybean aspirated grain fractions residue data have been fulfilled by a previously submitted soybean processing study (Memo, G. Kramer, 4/4/95; DP Barcode D208740). Because the composition of the fractions of the grain dust in the study was not comparable to commercial aspirated grain fractions and because the petitioner reported residue results for each fraction separately, the Agency calculated expected concentration factors in aspirated grain fractions of 73.8x for PMG and 57.5x for TMS.

Based on the highest average field trial (HAFT) residues from the soybean field trials and the calculated concentration factors, the expected residues in aspirated grain fractions are 1216 ppm [7.26 ppm PMG x 73.8 = 535.8 + 11.82 ppm TMS x 57.5 = 679.7]. Therefore, the proposed tolerance of 1300 ppm (of which no more than 720 ppm is trimethylsulfonium) for soybean aspirated grain fractions is appropriate. HED notes that the tolerance should be established for "Aspirated grain fractions." **A revised Section F is required.**

4.2.1g Processed Food/Feed (OPPTS GLN: 860.1520)

The processing data (MRID 43397004) indicate that residues of PMG and TMS concentrated 2.5x and 2.0x, respectively, in soybean hulls and did not concentrate in soybean meal and refined oil (<0.28X). The HAFT (total residues) from soybean field trials reflecting the maximum proposed use pattern is 19.08 ppm. Based on this HAFT and the observed average concentration factor (2.3x), the maximum expected total residues are 42.93 ppm for soybean hulls (of which no more than 23.64 ppm is trimethylsulfonium). Therefore, the proposed tolerance of 45 ppm (of which no more than 25 ppm is trimethylsulfonium) for soybean hulls will not be exceeded.

4.2.1h Water, Fish, and Irrigated Crops (OPPTS GLN 860.1400) - Not Applicable

4.2.1i Food Handling (OPPTS GLN 860.1460) - Not Applicable

4.2.1j Confined Accumulation in Rotational Crops (OPPTS GLN 860.1850)

HED has previously reviewed two confined rotational crop studies for sulfosate and concluded that rotational crop restrictions were not required (Memo, G. Kramer, 4/20/95).

4.2.1k Field Accumulation in Rotational Crops (OPPTS GLN 860.1900) - Not Applicable

4.2.1l Tolerance Reassessment Table - Not Applicable

4.2.1m Anticipated Residues (ARs)

The following ARs were included in the DEEM™ run:

Commodity	AR (ppm)
Soybeans	6.7
Refined soybean oil	1.9

Commodity	AR (ppm)
Soybean meal	1.9
Soybean protein isolate	1.9
Soybean flour	1.9

These values are based on the average field trial residue in soybean seed and the observed concentration factors. The AR for soybean meal was also used for soybean flour and protein isolate as residues appear to be localized in the seed coat.

4.2.1n International Harmonization of Tolerances

There is neither a Codex proposal, nor Canadian or Mexican limits for residues of glyphosate-trimesium in soybean and animal RACs. Therefore, a compatibility issue is not relevant to the proposed tolerances. (See Attachment 3: International Residue Limit Status.)

4.2.2 Dietary Exposure and Risk Analysis

A dietary exposure analysis using the Dietary Exposure Evaluation Model (DEEM™) was completed (Memo, S. Chun, 4/21/99; DP Barcode D254804) for acute and chronic (non-cancer) dietary exposure (See Attachment 4). The DEEM™ analysis evaluated the individual food consumption as reported by respondents in the USDA 1989-91 Continuing Surveys for Food Intake by Individuals (CSFII) and accumulated exposure to the chemical for each commodity.

Since the HED FQPA SFC reduced the 10x safety factor to 3x, the PAD, a modification of the acute or chronic RfD to accommodate the FQPA Safety Factor, was used in this risk assessment. The PAD is equal to the acute or chronic RfD divided by the FQPA Safety Factor. Therefore, the Agency's level of concern is for values >100% PAD .

For the acute dietary analysis, tolerance level residues, 100% crop treated (CT), and an aPAD of 0.3333 mg/kg/day were used. For the chronic dietary analysis, tolerance level residues, anticipated residue levels for soybean commodities based on field trial data (Memo, G. Kramer, 4/23/99; DP Barcode D243318), % CT information provided by BEAD (S. Smearman, 4/14/99), and a cPAD of 0.0333 mg/kg/day were used. Percent CT information was used for oranges, grapefruit, corn, peaches, and wheat. Crops that BEAD had estimated at 0 % CT (wheat, corn, and peaches) were rounded up to 1% CT. The registrant submitted a projected market share percent of 20% for soybeans. BEAD has concurred with this value (higher than the 2% in the BEAD quantitative usage data) (Personal communication to J. Kidwell from S. Smeraman, 4/21/99). Therefore, 20% was used in the chronic dietary analysis for soybeans.

Acute Dietary Exposure Analysis

The acute dietary exposure analysis estimates the distribution of single-day exposures for the U.S. population and certain subgroups and accumulates exposure to the chemical for each commodity. Each analysis assumes uniform distribution of sulfosate for the commodities on which sulfosate is used.

The acute dietary exposure analysis was performed for the U.S. population and 27 subgroups. Dietary exposures and associated acute risk at the 95th percentile are shown in Table 5. Besides the U.S. population, the subgroups included in Table 5 represent the highest dietary exposures for their respective subgroups (i.e., children, females, and also the other general population subgroup higher than U.S. population).

Table 5. Acute Dietary Exposure Results

Subgroups	Exposure (mg/kg/day)	% aPAD
U.S. Population	0.033377	10
Non-Hispanic Blacks	0.037008	11
All Infants (< 1 year)	0.140195	42
Females (13-19 yrs/not pregnant/not nursing)	0.024913	8

The Tier 1 acute dietary analysis for sulfosate is a highly conservative estimate of dietary exposure with the use of tolerance level residue values and 100% of the commodities assumed to be treated. The %aPADs were below HED's level of concern at the 95th percentile for the U.S. population and all subgroups, with the highest exposure of 42% aPAD in the subgroup All Infants (< 1 year). The results of this analysis indicate that the acute dietary risk associated with the amended use of sulfosate on soybeans is below the Agency's level of concern.

Chronic Dietary Exposure Analysis

The chronic DEEM™ dietary exposure analysis used mean consumption (3-day average). Dietary exposures for the U.S. population and other subgroups are presented in Table 6. The other subgroups included in Table 6 represent the highest dietary exposures for their respective subgroups (i.e., children, females, and also the other general population subgroup higher than U.S. population).

Table 6. Chronic Dietary Exposure Results

Subgroups	Exposure (mg/kg/day)	% cPAD
U.S. Population (48 states)	0.003078	9

Subgroups	Exposure (mg/kg/day)	% cPAD
Hispanics	0.003346	10
Children (1 - 6 years old)	0.008682	26
Females (13-19 years old, not pregnant/not nursing)	0.002643	8

The Tier 3 chronic dietary analysis for sulfosate is a more refined estimate with the use of some ARs and %CT information. However, it still is a high over-estimation of dietary exposure, since tolerance level residue values were used for the majority of the commodities. Further refinements would entail the use of ARs and/or monitoring data for all commodities. The %cPADs were below HED's level of concern for the U.S. population and all subgroups, with the highest exposure of 26% cPAD in the subgroup Children (1-6 years old). The results of this analysis indicate that the chronic dietary risk associated with the amended use of sulfosate on soybeans is below the Agency's level of concern.

4.2.3 Water

A DWLOC is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses. A DWLOC will vary depending on the toxic endpoint, with drinking water consumption, and body weights. Different populations will have different DWLOCs.

OPP uses DWLOCs internally in the risk assessment process as a surrogate measure of potential exposure associated with pesticide exposure through drinking water. In the absence of monitoring data for pesticides, it is used as a point of comparison against conservative model estimates of a pesticide's concentration in water.

DWLOC values are not regulatory standards for drinking water. They do have an indirect regulatory impact through aggregate exposure and risk assessments.

HED does not have monitoring data available to perform a quantitative drinking water risk assessment for sulfosate at this time. In a previous risk assessment (10-July-1998) for the use of sulfosate in/on corn, wheat, pome fruit, and soybeans, EFED provided ground and surface water exposure estimates for sulfosate at a maximum annual application rate of 4.75 lbs a.i./acre (Memo, J Carleton, S. Termes, 5/14/98; Barcode D243384, D2443314). For this risk assessment for the use of sulfosate on soybeans, HED estimated ground and surface water exposures using the values provided by EFED in the 5/14/98 memo and adjusting for the current maximum annual application rate of 8 lbs a.i./acre.

4.2.3a Ground Water

HED estimated a ground water concentration of **0.00377 ppb**. Using EFED's SCI-GROW ground water estimate of 0.00224 ppb at a maximum application rate of 4.75 lbs a.i./acre (Memo, J. Carleton, S. Termes, 5/14/98; Barcode D243384, D2443314), it is reasonable to assume that, based on the new maximum application rate of 8 lbs a.i./acre, the groundwater concentration will be proportional. Thus, for this risk assessment, the groundwater estimate was derived as follows: 0.00224 ppb x (8 lbs a.i.acre^{-1}/4.75 lbs a.i.acre^{-1}) = 0.00377 ppb.

4.2.3b Surface Water

HED estimated surface water concentrations of 211 ppb (acute) and 59 ppb (chronic). Using EFED's GENEEC surface water estimates of 125 ppb (acute) and 35 ppb (chronic) at a maximum application rate of 4.75 lbs a.i./acre (Memo, J. Carleton, S. Termes, 5/14/98; Barcode D243384, D2443314), it is reasonable to assume that, based on the new maximum application rate of 8 lbs a.i./acre, the surface water concentrations will be proportional. Thus, for this risk assessment, the surface water estimates were derived as follows:

Acute: 125 ppb x (8 lbs a.i. acre^{-1}/4.75 lbs a.i. acre^{-1}) = **211 ppb**
Chronic: 35 ppb x (8 lbs a.i. acre^{-1}/4.75 lbs a.i. acre^{-1}) = 59 ppb

According to OPP drinking water guidance (SOP 98.4), the 90/56-day GENEEC value may be divided by 3 to obtain a value for chronic risk assessment calculations. Therefore, the surface water value for use in the chronic risk assessment is **20 ppb**.

4.2.3c Drinking Water Risk

OPP has calculated acute and chronic DWLOCs and the results are listed in Table 7.

Table 7. Summary of Acute and Chronic DWLOC Calculations.

Population Subgroup	Food Exposure mg/kg/day	%PAD	Maximum Water Exposure mg/kg/day	Estimated Surface Water Conc. (ppb)	Estimated Ground Water Conc. (ppb)	DWLOC (ppb)
Acute Exposure (General Population, including infants and children)						
U.S. Population	0.033377	10	0.29996	211	0.00377	10,500
Non-Hispanic Blacks	0.037008	11	0.29633	211	0.00377	10,400
All Infants (<1 year)	0.140195	42	0.19314	211	0.00377	2,000
Females (13-19 yrs/np/nn)	0.024913	8	0.30842	211	0.00377	9,300

Population Subgroup	Food Exposure mg/kg/day	%PAD	Maximum Water Exposure mg/kg/day	Estimated Surface Water Conc. (ppb)	Estimated Ground Water Conc. (ppb)	DWLOC (ppb)
Chronic Exposure						
U.S. Population (48 states)	0.003078	9	0.03026	20	0.00377	1,060
Hispanics	0.003346	10	0.02999	20	0.00377	1,050
Children (1-6 years old)	0.008682	26	0.02465	20	0.00377	250
Females (13-19 yrs/np/nn)	0.002643	8	0.03069	20	0.00377	920

To calculate a DWLOC for an exposure (acute or chronic) relative to a toxicity endpoint, the dietary food exposure (from DEEM) was subtracted from the PAD to obtain the acceptable exposure to sulfosate in drinking water. DWLOCs were then calculated using the following default body weights and drinking water consumption figures, which are listed in Table 8.

Table 8. Default Body Weight and Drinking Water Consumption Figures

DEEM Population	Body Weights (kg)	Drinking Water Consumption (liters/day)
U.S. Population/48 States	70	2
Females 13+	60	2
Infants/children	10	1

Calculation (for acute and chronic exposures):

$$DWLOC\ (\mu g/L) = \frac{water\ exposure\ (mg/kg/day)\ x\ (body\ weight)}{consumption\ (L)\ x\ 10^{-3}\ mg/\mu g}$$

The estimated average concentrations of sulfosate in surface water are **211 ppb** (acute exposure) and **20 ppb** (chronic exposure). The estimated average concentration of sulfosate in groundwater is **0.00377 ppb.** The estimated acute and chronic concentrations of sulfosate in surface water and groundwater are less than OPP's DWLOCs for sulfosate as a contribution to acute and chronic aggregate exposure.. Therefore, taking into account the present uses and uses proposed in this action, OPP concludes with reasonable certainty that residues of sulfosate in drinking water (when considered along with other sources of exposure for which OPP has reliable data) would not result in unacceptable levels of acute or chronic aggregate human health risk at this time.

OPP bases this determination on a comparison of estimated concentrations of sulfosate in surface waters and ground waters to back-calculated DWLOCs for sulfosate. These DWLOCs were determined after OPP has considered all other non-occupational human exposures for which it has reliable data, including all current uses, and uses considered in this action. The estimates of sulfosate in surface waters are derived from water quality models that use conservative assumptions (health-protective) regarding the pesticide transport from the point of application to surface and ground water. Because OPP considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, DWLOC may vary as those uses change. If new uses are added in the future, OPP will reassess the potential impacts of sulfosate on drinking water as a part of the aggregate risk assessment process.

5.0 AGGREGATE RISK ASSESSMENT

Because there are no proposed residential uses of sulfosate that will result in post-application residential exposure, aggregate exposure risk assessment will be limited to food and water only. The aggregate acute and chronic risk estimate will be based on the exposure from food and water only for the most highly exposed population subgroups and the general population as appropriate. Details concerning the assumptions used in deriving exposure estimates and risk characterizations were discussed previously in this document.

5.1 Acute Aggregate Risk

Acute risk estimates associated with aggregate exposure to sulfosate in food and water do not exceed HED's level of concern. The Tier 1 acute dietary analysis for sulfosate is a highly conservative estimate of dietary exposure with the use of tolerance level residue values and 100%CT. For the U.S. population, 10% of the aPAD is occupied by dietary (food) exposure. For the most highly exposed subgroup, All Infants (< 1 year), 42% of the aPAD is occupied by dietary (food) exposure. Thus, the percent aPADs were below HED's level of concern at the 95th percentile for the U.S. population and all subgroups. The maximum estimated concentrations of sulfosate in surface and ground water are less than OPP's DWLOCs for sulfosate as a contribution to acute aggregate exposure. Therefore, OPP concludes with reasonable certainty that residues of sulfosate in drinking water do not contribute significantly to the acute aggregate human health risk at the present time considering the present uses and the uses proposed in this action.

OPP bases this determination on a comparison of estimated concentrations of sulfosate in surface waters and ground waters to levels of concern for sulfosate in drinking water. The estimates of sulfosate in surface and ground waters are derived from water quality models that use conservative assumptions regarding the pesticide transport from the point of application to surface and ground water. Because OPP considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, levels of concern in drinking water may

vary as those uses change. If new uses are added in the future, OPP will reassess the potential impacts of sulfosate on drinking water as a part of the acute aggregate risk assessment process.

5.2 Chronic Aggregate Risk

Chronic risk estimates associated with aggregate exposure to sulfosate in food and water do not exceed HED's level of concern. The Tier 3 chronic dietary analysis for sulfosate is a more refined estimate with the use of some anticipated residues (ARs) and %CT information. For the U.S. population, 9% of the cPAD is occupied by dietary (food) exposure. For the most highly exposed subgroup, Children (1-6 years old), 26% of the cPAD is occupied by dietary (food) exposure. Thus, the %cPADs were below HED's level of concern. The estimated average concentrations of sulfosate in surface and groundwater are less than OPP's levels of comparison for sulfosate in drinking water as a contribution to chronic aggregate exposure. Therefore, OPP concludes with reasonable certainty that residues of sulfosate in drinking water do not contribute significantly to the chronic aggregate human health risk at the present time considering the present uses and uses proposed in this action.

OPP bases this determination on a comparison of estimated concentrations of sulfosate in surface waters and ground waters to levels of comparison for sulfosate in drinking water. The estimates of sulfosate in surface and ground waters are derived from water quality models that use conservative assumptions regarding the pesticide transport from the point of application to surface and ground water. Because OPP considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, levels of concern in drinking water may vary as those uses change. If new uses are added in the future, OPP will reassess the potential impacts of sulfosate on drinking water as a part of the aggregate chronic risk assessment process.

5.3 Short- and Intermediate-Term Aggregate Risk

Since there are no residential uses or exposure scenarios, short- and intermediate-term aggregate risk assessments were not conducted.

5.4 Long-Term Aggregate Risk

Since there are no residential uses or exposure scenarios, a long-term aggregate risk assessment was not conducted.

6.0 DATA NEEDS

6.1 Chemistry

- Revised Section F

6.2 Toxicology

- A **developmental neurotoxicity study** is required based on the weight-of-evidence for concerns of neurotoxicity in the mouse oncogenicity study, the subchronic feeding studies in dogs, 21-day dermal toxicity study in rats, and acute and subchronic neurotoxicity studies in rats. See Section 3.2 (FQPA Considerations) for more details.

6.3 Occupational Exposure

- A revised Section B should be submitted. The label indicates a REI of 4 hours. However, sulfosate does not meet the criteria set forth in the Reduced Reentry Interval for Low Risk Pesticides (4/1995) due to the fact that it has neurotoxic effects. Therefore, the appropriate REI for this chemical is 12 hours. (Memo, M. Copley, G. Kramer, J. Cruz, 7/10/98; DP Barcode D242550)

7.0 ATTACHMENTS

- Attachment 1: SULFOSATE - Second Report of the Hazard Identification Assessment Review Committee (HIARC) (M. Copley and J. Rowland, HED Doc. No. 012652, 6/25/98)

- Attachment 2: Report of the FQPA Safety Factor Committee (B. Tarplee and J. Rowland, HED Doc. No. 012681, 6/29/98)

- Attachment 3: International Residue Limit Status

- Attachment 4: Glyphosate-trimesium (sulfosate) - Dietary Exposure Analysis for Sulfosate. (S. Chun, 4/22/99)

cc with attachments: PP# 7F04854, J. Kidwell (RAB1), S. Chun (RAB1), D. Vogel (RAB1), G. Kramer (RAB1)
RDI: M. Morrow (4/30/99); Team 1 (4/26/99); G. Kramer (4/ 26/99)
J. Kidwell:806S:CM2(703)305-7472:7509C:RAB1

Attachment 1: SULFOSATE - Second Report of the Hazard Identification Assessment Review Committee (HIARC) (M. Copley and J. Rowland, HED Doc. No. 012652, 6/25/98)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

012652

DATE: **June 25, 1998**

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: ***SULFOSATE*** **- Second Report** of the Hazard Identification Assessment Review Committee.

FROM: Marion Copley, D.V.M., D.A.B.T. for Mc 6/25/98
Registration Action Branch 1
Health Effects Division (7509C)
and
Jess Rowland, Executive Secretary 6/25/98
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

THROUGH: K. Clark Swentzel, Chairman, K. Clark Swentzel 6/25/98
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
and
Mike Metzger, Co-Chairman
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Melba Morrow, Branch Senior Scientist
Registration Action Branch 1
Health Effects Division (7509C)

PC Code: 128501

On June 12, 1998 the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) met to reexamine the neurotoxicity hazard assessment/characterization for **Sulfosate**. This was a follow-up meeting to the HIARC meeting held on April 26, 1998 to re-assess the Reference Dose (RfD) established in 1994 as well as the toxicological endpoints selected for acute dietary and occupational/residential exposure risk assessments for **Sulfosate**. The HIARC addressed the potential enhanced sensitivity of infants and children from exposure to sulfosate as required by the Food Quality Protection Act (FQPA) of 1996 at both meetings. This report includes the Committee's conclusions from both meetings.

Committee Members in Attendance

Members present were: Karl Baetcke, Bill Burnam, Robert Fricke. Sue Makris, Melba Morrow, Jess Rowland (Executive Secretary) and Clark Swentzel (Chairman). Member(s) in absentia: Karen Hammernik, Mike Metzger and John Redden. Data were presented by Marion Copley of the Registration Action Branch 1 and Kathleen Raffaele of the Toxicology Branch 2.

Data Presentation:
and
Report Preparation

Marion Copley 6/25/98

Marion Copley, D.V.M., D.A.B.T.

Report Concurrence:

6/25/98

Jess Rowland
Executive Secretary

I. INTRODUCTION

On April 26, 1998 the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) re-assessed the Reference Dose established in 1994, selected the toxicological endpoints for acute dietary as well as occupational and residential exposure risk assessments, and addressed the potential enhanced sensitivity of infants and children from exposure to sulfosate as required by the Food Quality Protection Act (FQPA) of 1996.

In a follow-up meeting held on June 12, 1998 the HIARC reexamined the neurotoxicity studies for better characterization of the neurotoxic potential of **Sulfosate.** This report includes information from both meetings.

II. HAZARD IDENTIFICATION

A. Acute Reference Dose (RfD)

Study Selected: Acute Rat Neurotoxicity **Guideline #: 81-8**

MRID No.: 43132301

Executive Summary: In an acute neurotoxicity study, Glyphosate Trimesium Technical (purity 59.4%, Lot No. F47 D7534/36) was used to treat Alpk:APfsD rats, 10/sex/dose by gavage at 1 ml/100 g bw with doses of 0, 30, 100 or 300 mg/kg. Adequate positive control data was provided. At **300 mg/kg** there was death, ptosis, decreased activity, decreased splay reflex, upward curvature of spine, chromodacryorrhea, staining around the nose, decreased bodyweight and food consumption (males), shaking, sides pinched in, signs of urinary incontinence, irregular breathing, hunched posture, abnormal or staggering gait, increased time to tail flick, decreased landing foot splay, decreased forelimb grip strength, decreased hindlimb grip strength, decreased motor activity. There was no microscopic evidence of neurotoxicity. There were no indications of neurotoxicity below a lethal dose. **The LEL was 300 mg/kg based on mortality, neurologic signs described above and decreased body weight and food consumption. The NOEL was 100 mg/kg.**

Dose and Endpoint for Risk Assessment: NOEL = 100 mg/kg based on mortality, decreased body weight and food consumption, and neurotoxicity at 300 mg/kg (LOEL).

Uncertainty Factor: 100 (10 x for inter-species extrapolation and 10 x for intra- species variations)

$$\textbf{Acute RfD} = \frac{\textbf{100 mg/kg}}{\textbf{100 (UF)}} = \textbf{1.0 mg/kg}$$

Comments about Study and Endpoint: This endpoint is appropriate for this risk assessment, since it was observed after a single dose in the acute neurotoxicity study.

This risk assessment is required.

B. CHRONIC DIETARY [Reference Dose (RfD)]

Study Selected: One-Year Chronic Dog Study **Guideline #:** 83-1b

MRID Nos.: 40214005 and 41235902

Executive Summary: In a chronic oral gavage study, beagle dogs (5/sex/dose) were treated with sulfosate (SC-0224 (batch # EHC 0469-15;WRC# 8108-24-1; 56.2% pure)) for 1 year at doses of 0, 2,10, or 50 mg kg/day. Signs of toxicity were limited to the 50 mg/kg/day group females and included transient salivation (1/5 at 10 mg/kg/day and 5/5 at 50 mg/kg/day) and emesis (single episodes in 3/5 dogs). The decreased LDH in females (53, 41, 32, 15*, from control to high dose) at 12 months is of questionable biological significance. The high dose was however, supported by subchronic studies where transient salivation and emesis again occurred at 50 mg/kg/day in a 90 day study and at 75 mg/kg/day in a 28 day study; with death occurring within 3 days at 150 mg/kg/day in the 28 day study. **The LOEL is 50 mg/kg/day based on salivation and emesis and support from shorter term studies also with emesis and salivation. The NOEL is 10 mg/kg/day.**

Dose and Endpoint for Risk Assessment: NOEL =10 mg/kg/day based on salivation and emesis at 50 mg/kg/day (LOEL).

Uncertainty Factor: 100 (10 x for inter-species extrapolation and 10 x for intra- species variation).

$$\textbf{Chronic RfD} = \frac{10\ \text{mg/kg/day}}{100(\text{UF})} = \textbf{0.10 mg/kg/day}$$

Comments about Study and Endpoint: The HIARC concurs with the RfD established in 1994.

This risk assessment is required.

C. Occupational/Residential Exposure

1. Dermal Absorption: There are no dermal absorption studies available for review.

Dermal Absorption Factor: Dermal absorption factor is not applicable since no toxicological endpoints were identified for dermal risk assessments.

2. Short-Term Dermal - (1-7 days)

Study Selected: None

MRID No.: None

Executive Summary: None

Dose and Endpoint: Not Applicable

Comments about Study/Endpoint: The database included a 21-day dermal toxicity study with the technical product and another 21-day dermal toxicity study with the formulation product. In the study with the technical product, for systemic toxicity, the NOEL was 1000 mg/kg/day (Limit-Dose), the highest dose tested; a LOEL was not established. In the study with the formulation product, the NOEL was 250 mg/kg/day and the LOEL was 1000 mg/kg/day based on minimal sciatic nerve fiber degeneration of unstated severity. The Committee determined that the potential for risk via the dermal route is minimal based on: 1) the low dermal/systemic toxicity demonstrated in the 21-dermal toxicity studies (discussed below);2) the current use patterns (agricultural) do not indicate an exposure concern; and 3) there are no registered residential uses at the present time. **At this time dermal risk assessments are not required. However, if residential uses, are requested or there is a residential post application exposure, the issue of dermal risk assessment will need to be reexamined.**

No systemic toxicity was seen following 15 repeated dermal application of the technical material [57.3%] at doses of 0, 10, 100, and 1000 mg/kg/day, 6 hours /day, 5 days/week over a 3 week period to male and female rabbits. For systemic toxicity, the NOEL was 1000 mg/kg/day (Limit Dose). There was mild erythema at the application sites in all of the treatment groups (MRID No.4089702).

In another 21-day dermal toxicity study, male and female Wistar rats received repeated dermal applications of the formulation product Touchdown [4 LCE formulation, 39.8%] at 0, 25, 250, or 1000 mg/kg/day for 6 hours/day, for 21 days. At 25 and 1000 mg/kg/day, but not at 250 mg/kg/day, there was slight increases in testes weight with no microscopic changes. There were no effects at 250 mg/kg/day. At 1000 mg/kg/day, there were skin irritation effects and occasional sciatic nerve fiber degeneration of unstated severity [1/5 males and 2/5 females]. These effects were not observed in controls. For systemic toxicity, the NOEL was 250 mg/kg/day and the LOEL was 1000 mg/kg/day based on sciatic nerve findings at 1000 mg/kg/day (MRID No.41209904).

This risk assessment is **NOT** required at this time.

2. Intermediate-term Dermal (1-Week to Several Months)

Study Selected: None

MRID No.: None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not Applicable

Comments about Study and Endpoint: **At this time dermal risk assessments are not required. However, if residential uses, are requested or there is a residential post application exposure, the issue of dermal risk assessment will need to be reexamined** (See Short-Term Dermal for details).

This risk assessment is **NOT** required at this time.

3. Long-term Dermal (Several Months to Lifetime)

Study Selected: None

MRID No.: None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not applicable

Comments about Study and Endpoint: **At this time dermal risk assessments are not required. However, if residential uses, are requested or there is a residential post application exposure, the issue of dermal risk assessment will need to be reexamined.** (See Short-Term Dermal for details).

This risk assessment is **NOT** required at this time.

4. Inhalation Exposure (All Time periods).

Except for an acute inhalation toxicity study no other inhalation studies are available in the toxicology data base.

Based on the high inhalation exposure potential for proposed use patterns, HIARC selected oral NOELs for inhalation risk assessments. Since an oral dose is used, risk assessments should follow the route-to-route extrapolation as below:

Step 1 The inhalation exposure component (i.e. ug a.i/L./day) using 100% absorption rate (default value) and application rate should be converted to an **equivalent oral dose** [mg/kg/day].

Step II The converted dose should then be compared to the oral NOELs to calculate the MOEs. The NOELs are as follows:

For Short-Term:	NOEL = 100 mg/kg/day
For Intermediate-term:	NOEL = 10 mg/kg/day
For Chronic Exposures	NOEL = 10 mg/kg/day

These NOELs were also used for establishing the acute and chronic RfDs.

This risk assessment is required.

D. Margins of Exposure for Occupational/Residential Exposures

Margins of exposure (MOEs) are not required for occupational/residential exposure risk assessments since toxicological endpoints were not selected for these exposure scenarios. A MOE of 100 is acceptable for inhalation risk assessments (any time period). If the use pattern changes and a dermal risk assessment is required, a MOE of 100 is adequate (any time period).

E. Recommendation for Aggregate Exposure Risk Assessments

Not required; there are no registered residential uses at the present time.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No. 40214007, 41209905, 41209907

Discussion of Tumor Data: No evidence of carcinogenicity.

Adequacy of the Dose Levels Tested: Doses tested were 0, 0, 100, 500, or 1000 ppm for 24 months in Sprague-Dawley rats. Palatability problems were observed in that food consumption and body weight were both decreased at 1000 ppm. Results from subchronic studies indicate that at least ½ MTD was used in the 2-year rat study. It was believed that the chemical was adequately tested for carcinogenicity.

2. Carcinogenicity Study in Mice

MRID No. 40214006, 41209907

Discussion of Tumor Data No evidence of carcinogenicity.

Adequacy of the Dose Levels Tested Doses were 0, 100, 1000, or 8,000 ppm in CD-1 mice. Decreased body weight and food consumption occurred at 8,000 ppm, and duodenal hyperplasia in females at 8,000 ppm.

3. Classification of Carcinogenic Potential: The HED/RfD Committee (document dated 26-JUL-1994) has classified sulfosate as a "Group E" - no evidence of carcinogenicity in male and female rats as well as in male and female mice. The current HIARC Committee saw no reason to modify this decision.

IV. FQPA CONSIDERATIONS

1. Adequacy of the Database:

Acceptable hen delayed neurotoxicity, acute and subchronic rat neurotoxicity screening studies have been submitted to the Agency. Acceptable prenatal toxicity studies in rats and rabbits and a 2-generation reproductive toxicity study in rats on sulfosate have been submitted to the Agency. However, a developmental neurotoxicity is required based on the neurotoxicity observed in dogs, rats and mice (see below).

2. Neurotoxicity Data:

Sulfosate has evidence of neurotoxicity in several studies in rats, dogs and the mice.

The following three executive summaries present the relevant findings from acceptable hen and rat (acute and subchronic) neurotoxicity studies. Following that, are brief summaries of other sulfosate studies with signs of neurotoxicity. Following these summaries is the characterization of the neurotoxicity issues raised by the data base.

81-7 Hen delayed neurotoxicity study - In an acute neurotoxicity study (MRID 43151201), white leghorn chickens (6 hens/group in control groups, 8 hens/group in treated groups) were treated with Tech ICIA-0224 (purity: 56.9%, Lot No.4921-50-2; 8289-35-1) by gavage at doses of 0, 500 or 5000 mg/kg in 5 ml/kg water. TOCP (500 mg/kg) was the positive control. Each animal was dosed twice during the study; day 1 and day 22. Each animal was evaluated up to day 41 (or 42). At 500 mg/kg there was diarrhea starting a few days after each dosing, lasting for 2-3 days. At 5000 mg/kg there was diarrhea, changes in comb appearance, early decreased food consumption and decrease in egg production. No

indications of delayed neurotoxicity were observed. The positive control indicated the appropriate clinical signs of toxicity, increased ataxia and microscopic observations for an organophosphate. **The NOEL for systemic toxicity was 500 mg/kg. The LEL for systemic toxicity was 5000 mg/kg.**

81-8 Acute Neurotoxicity Study - In an acute neurotoxicity study (MRID 43132301), *Glyphosate Trimesium Technical (purity 59.4%)* was used to treat Alpk:APfsD rats, 10/sex/dose by gavage at 1 ml/100 g bw with doses of 0, 30, 100 or 300 mg/kg. Adequate positive control data was provided. At 300 mg/kg there was death, ptosis, decreased activity, decreased splay reflex, upward curvature of spine, chromodacryorrhea, staining around the nose, decreased bodyweight and food consumption (males), shaking, sides pinched in, signs of urinary incontinence, irregular breathing, hunched posture, abnormal or staggering gait, increased time to tail flick, decreased landing foot splay, decreased forelimb grip strength, decreased hindlimb grip strength, decreased motor activity. There was no microscopic evidence of neurotoxicity. There were no indications of neurotoxicity below a lethal dose.. **The LEL was 300 mg/kg based on mortality, neurologic signs described above and decreased body weight and food consumption. The NOEL was 100 mg/kg.**

82-7 Subchronic Neurotoxicity Screening Battery - Technical glyphosate trimesium (sulfosate, 59.4%, Batch Lot No. F47 D7534/36; CTL Y06380/036) was tested in a 90 day neurotoxicity feeding study (MRID 43151202) in Alpk:APfSD rats. Rats (12/sex/group) received either 0, 200, 600, or 2000 ppm (0, 15.6, 47.6 or 153.2 mg/kg/day for males; 0, 18.2, 54.4 or 171.0 mg/kg/day for females) in diet. Six/sex/dose group received complete necropsy and neurohistopathology. Positive control data were provided.. Clinical signs of toxicity, body weights, food consumption, functional battery, motor activity and neuropathology parameters were measured and recorded regularly. Positive control data were provided. At **2000 ppm**, decreased body weights (16% for males and 9% for females), food consumption and utilization were observed. In addition, mean forelimb grip strength values for high dose females were statistically significantly decreased over the control values during weeks 5-14 (75 - 82% of controls). There was no microscopic evidence of neurotoxicity. The significance of the decreased grip strength as a neurotoxicological effect is less certain since there were no effects in mean hindlimb grip strength for high dose females, in either of the mean grip strength values at any time period for males, in any of the other functional battery parameters, in motor activity values or in neuropathology microscopic examinations for either sex. However, it did occurred at all time points, was statistically significant, and signs of neurotoxicity occur in other studies **The LEL is 2000 ppm (153.2 mg/kg/day) based on decreases in mean body weight, food consumption, food utilization and mean forelimb grip strength values. The NOEL is 600 ppm (47.6 mg/kg/day).**

The following neurotoxic effects were seen following exposure to sulfosate for varying durations in several species.

A. Dogs

1. In a 28-day gavage study (summary only available), clinical signs (decreased activity, emesis, salivation, tremors and/or shaking) were seen at 36 mg/kg/day, with the NOEL at 20 mg/kg/day. Details of incidence (number of animals or persistence) and severity of effects was not included in the summary.

2. In a 90-day gavage study (MRID 41209903, 4163301), salivation and emesis were seen in both sexes in a dose-related manner (incidence for emesis was 1, 2, 3, 6 for males, 4, 0, 3, 6 for females at 0, 2, 10, and 50 mg/kg/day, respectively; incidence for salivation (transient) was 0, 0, 1, 3 for males, 0, 0, 0, 5 for females). First day of observation was earlier for high dose groups, but the number of observed incidences was not included in the DER. In addition, dilated lateral ventricles (brain) were observed in 2 high dose females macroscopically, and hydrocephalus was observed in one high dose female microscopically. [n=6/sex/group]

3. In a 90-day capsule study (MRID 44246704 - preliminary review), increased incidence of salivation at dosing was seen in two high dose males (total of 92 observations from weeks 2-14 compared to 3 observations in 1 animal from weeks 10-13 in control group); in addition, salivation was observed 15 times in 2 high dose males unrelated to dosing, with no observations in any other group. Increased incidence of salivation at dosing was also seen in high dose females (105 observations in 3 animals from weeks 4-14, no observations in any other group); salivation unrelated to dosing was also increased (32 observations in 2 animals from weeks 3-13). One high dose female was sacrificed in extremis on day 2 (the animal was found cold, recumbent, and comatose), and the dose was reduced in one high dose female who displayed multiple symptoms (tremors, recumbency, paddling of limbs) at two or three separate time points during the study (weeks 5, 7, and 11). On these occasions, the occurrence of symptoms was preceded by increased severity of salivation; dosing was stopped at the appearance of symptoms. When symptoms resolved, dosing was resumed, but symptoms recurred. After the second appearance of symptoms and dosing discontinuation, dosing was resumed at a lower level (40 mg/kg/day); severe symptoms did not recur at that dose level, but did recur when dosing was briefly returned to the 50 mg/kg/day level. Dosing was then resumed at 40 mg/kg/day to study termination. Upon pathological evaluation, hydrocephalus was found in one high dose male, a different high dose male had unilateral cataract, and GI muscle hypertrophy was seen in a third high dose male. [Doses were 0, 10, 25, or 50 mg/kg/day; n=4/sex/group].

4. In a one year gavage study (MRID 40214005), 'transient salivation' was observed in one mid-dose female and 5 high dose females (no specific incidence information was provided in the DER). On histopathological evaluation, hydrocephalus was found in one high dose male and one mid-dose female. [Doses were 0, 2, 10, and 50 mg/kg/day, n=5/sex/group].

B. Mice

1. In a 2-year oncogenicity study in mice (MRID 40214006), there was increased incidence of lumbar spinal white matter degeneration in males only, as follows (incidence given as percent): 2, 2, 4, 4, 8% for 2 control groups, 100, 1000, 8000 ppm groups respectively. The increased incidence of white matter degeneration was statistically significant, and was used to set the LOEL for males for the study at the high dose, with the NOEL at 1000 ppm.

C. Rats

1. Developmental toxicity (MRID 00126618, 00132183, 00155387): The maternal NOEL was 100 mg/kg/day, based on decreased body weight gain, decreased food intake, and clinical signs (salivation [7/20], lethargy [8/20], and chromorhinorrhea [9/20]) at 333 mg/kg/day. Incidences of clinical signs in controls were 0/24 for salivation, 0/24 for lethargy, and 2/24 for chromorhinorrhea. [Doses were 0, 30, 100, 333 mg/kg days 6-20 of gestation, by gavage].

2. 21-day dermal toxicity (MRID 41209904): In a 21-day dermal toxicity study, sciatic nerve degeneration was seen in 1/5 high dose males and 2/5 high dose females. [Doses were 0, 25, 250, and 1000 mg/kg, 6 hrs./day for 21 days, n=5/sex/group, histopathology was conducted on control and high dose groups only].

D. Neurotoxicity Characterization

Sulfosate is a neurotoxic chemical, which produces clinical findings such as **salivation**, tremors, emesis, decreased activity in dogs and/or rats. Salivation was the most consistent sign, and in dogs may have served as a precursor to more severe symptoms. In one study, salivation stopped upon withdrawal of sulfosate and recurred upon reintroduction of treatment.. Dogs appear to be the most sensitive species for these effects, with high intra-individual variability in sensitivity. Acute neurotoxicity effects observed after a single dose of 300 mg/kg in the rat included ptosis, decreased activity, decreased splay reflex, upward curvature of spine, shaking, sides pinched in, signs of urinary incontinence, irregular breathing, hunched posture, abnormal or staggering gait, increased time to tail flick, decreased landing foot splay, decreased forelimb grip strength, decreased hindlimb grip strength, decreased motor activity. There was also death at this dose. In the subchronic rat neurotoxicity study, the decreased forelimb grip strength observed at 153 mg/kg/day, in females only, may also have been due to treatment. **Hydrocephalus** or dilated ventricles were observed in at least one animal at the HDT (50 mg/kg/day) in adult dogs in all the dog studies, following both 90-days (gavage or capsule) and one year of dosing. This finding was never seen in controls or low dose groups. Hydrocephaly and/or dilated ventricles in dogs of this age may have been due to inherent asymptomatic incidences in the beagle (Vullo et al.,

1997), but it was noted that these animals were not supplied by the same breeding colony, and the incidences were only observed at the high dose levels across several studies. Therefore, it was agreed by the Committee that these findings could not be dismissed. **Neuropathology** was observed in the 21-day rat dermal study (sciatic nerve degeneration) at 1000 mg/kg, and the 2-year chronic mouse study (degeneration of the sciatic nerve, lumbar spinal root, and lumbar spinal white matter in males) at 991 mg/kg. Although these findings were previously discounted due to lack of supporting neuropathology data in the acute and subchronic neurotoxicity studies in rats, the overall neurotoxicity profile of the chemical indicated that the neuropathology could be a treatment-related effect of concern.

3. Developmental Toxicity Data

83-3a Prenatal Developmental Study - Rat - In a developmental toxicity study (MRID 00132183), rats (25/dose) were treated with sulfosate (SC-0224 19.2% ai; Lot No. EHC-0355-25), by gavage on gestation days 6 through 20 at dose levels of 0, 30, 100, or 333 mg/kg/day. The test material was dissolved in water and administered in a volume of 5 ml/kg. Treatment related effects were limited to the high dose dams and included decreased body weight (17 % less than the control), body weight gain and feed consumption. There was also salivation, chromorhinorrhea and lethargy after dosing in this group ($p < 0.05$). **The Maternal LOEL is 333 mg/kg/day based on decreased body weight, feed consumption and body weight gain along with increased incidences of salivation, chromorhinorrhea, and lethargy after dosing. The Maternal NOEL is 100 mg/kg/day.** Developmental signs of toxicity were limited to the high dose and included decreased fetal body weight (5.0, 4.9, 4.9, 4.2* gm, controls to high dose). **The Developmental toxicity LOEL is 333 mg/kg/day based on decreased fetal body weight. The Developmental toxicity NOEL is 100 mg/kg/day.**

83-3b Prenatal Developmental Study - Rabbit - In a developmental toxicity study (MRID 00155526), New Zealand white rabbits (15/group except 21 at the high dose) were treated by gavage with sulfosate (SC-0224, purity: 56.2%, Lot No. EHC-0355-25) from gestation days 7 - 19. The test material was dissolved in water and administered in a volume of 2 ml/kg at dose levels of 0, 10, 40 or 100 mg/kg/day. **The Maternal LOEL is 100 mg/kg/day (6 deaths in 17 pregnant doses, 4 abortions in the 11 survivors along with decreased body weight, feed consumption and body weight gain). The Maternal NOEL is 40 mg/kg/day.**

The developmental LOEL is 100 mg/kg/day based on decreased number of live fetuses/doe for 7 surviving rabbits (5.4 versus 7.4 in controls), 4 rabbits aborted their litters. Having only 7 litters does not give a sufficiently higher number of animals to absolutely conclude that no developmental toxicity is occurring, particularly in light of the massive losses to death and abortions. The developmental NOEL is 40 mg/kg/day.

4. Reproductive Toxicity:

83-4 Two-Generation Reproduction Study - Rat - In a 2-generation reproduction study (MRID 00154273), 20 male and 30 female/group Sprague-Dawley rats received sulfosate (SC-0224 tech. Purity: 19.2% a.i.) at dose levels of 0, 150, 800, or 2000 ppm in the diet (average for P0 and P1 - males - 0, 6.0, 35, 88.5 mg/kg/day; females - 0, 8, 41, 98 mg/kg/day). **The systemic LEL is 800 ppm (35 and 41 for males and females) based on a decrease in absolute and sometimes relative organ weights in both generations (thymus, heart, kidney and liver) at 800 and 2000 ppm and a decrease in body weights and body weight gains during the premating period at 2000 ppm. The Systemic NOEL: 150 ppm (6 and 8 for males and females).**

The reproductive/developmental LOEL is 800 ppm (35 and 41 for males and females) is based on decreased litter size in F0a and F1b litters at 2000 ppm and on decrease in *mean pup weights during lactation in second litters at 800 ppm & in all litters at 2000* ppm. The reproductive/developmental NOEL is 150 ppm (6 and 8 for males and females).

5. Determination of Susceptibility

The data provided no indication of increased susceptibility in rats or rabbits from in utero and/or post natal exposure to sulfosate. In the prenatal developmental toxicity study in rats, evidence of developmental toxicity was seen only in the presence of maternal toxicity. In the developmental toxicity study in rabbits, developmental toxicity was seen in the presence of maternal toxicity at the highest dose level. In the two-generation reproduction study in rats, effects in the offspring were observed only at or above treatment levels which results in evidence of parental toxicity. It should be noted that a developmental neurotoxicity study is required.

6. Recommendation for a Developmental Neurotoxicity Study

The following is a result of the HIARC reevaluation of the neurotoxicity hazard assessment and need for a developmental neurotoxicity study the meeting dated 12-JUN-1998.

The following information was considered in support of need for a developmental neurotoxicity study for sulfosate. Based upon a weight of evidence consideration of all these factors, the Committee decided **to require the conduct of a developmental neurotoxicity study with sulfosate** to evaluate the potential for effects on functional development

a) Evidence that support requiring a developmental neurotoxicity study:

» Sulfosate is a neurotoxic chemical (details are described in the summary document), which produces clinical findings such as salivation, tremors, emesis, decreased activity in dogs and/or rats. Acute neurotoxic effects were observed after a single dose of 300

mg/kg in the rat.

» Hydrocephalus or dilated ventricles were observed at the HDT (50 mg/kg/day) in adult dogs following 90-days (gavage or capsule) or 1-year of dosing. Hydrocephaly and/or dilated ventricles in dogs of this age may have been due to inherent asymptomatic incidences in the beagle (Vullo et al., 1997), but it was noted that these animals were not supplied by the same breeding colony, and the incidences were only observed at the high dose levels across several studies. Therefore, it was agreed by the Committee that these findings could not be dismissed.

» Neuropathology was observed in the 21-day rat dermal study (sciatic nerve degeneration) at 1000 mg/kg, and the 2-year chronic mouse study (degeneration of the sciatic nerve, lumbar spinal root, and lumbar spinal white matter in males) at 991 mg/kg. Although these findings were previously discounted due to lack of supporting neuropathology data in the acute and subchronic neurotoxicity studies in rats, the overall neurotoxicity profile of the chemical indicated that the neuropathology could be a treatment-related effect of concern.

b) Evidence that do not support asking for a developmental neurotoxicity study:

» No evidence of treatment-related anomalies in the development of the fetal nervous system were observed in the prenatal developmental toxicity studies in either rats or rabbits, at maternally toxic oral doses up to 333 or 100 mg/kg/day, respectively. In the rat study, anomalies of the brain were observed in all groups, including control, at similar incidences (dilation of the 4th ventricle), or only in low- or mid-dose. In the rabbit study, dilation of the 4th ventricle was seen at all dose levels except for the HDT and at a higher incidence in controls; hydrocephalus was observed at a non-treatment-related distribution (1/1/0/2 fetuses).

» No clinical observations indicative of neurobehavioral or functional abnormalities were reported for pups or second generation (F1) adults in the two-generation reproduction study in rats.

» No effects on brain weight were observed in any of the guideline studies in which these parameters were measured.

» No evidence of cholinesterase inhibition was observed for sulfosate.

» Sulfosate is not a potent toxicant; it has an oral LD_{50} of 750 mg/kg in rats.

» SAR: glyphosate, a related chemical, is not neurotoxic

7. Determination of the FQPA Safety Factor:

The determination of the FQPA safety factor is referred to the FQPA Safety Factor Committee. The weight of the evidence should take into account the lack of evidence of susceptibility in acceptable studies as well as the requirement for a developmental neurotoxicity study.

8. Additional information from the literature (IF AVAILABLE) None

V. DATA GAPS

There are no data gaps for the standard Subdivision F Guideline requirements for a food-use chemical by 40 CFR Part 158, however a developmental neurotoxicity study in the rat is required.

VI. HAZARD CHARACTERIZATION

Sulfosate is a herbicide, which consists of trimethylsulfonium glyphosate. The cationic component is trimesium and the anionic component is glyphosate. The toxicology data base provides no evidence that sulfosate has anticholinesterase activity, as evidenced by decreased cholinesterase activity in rats and dogs following subchronic and chronic exposures.

In acute toxicity studies, sulfosate exhibits low to high toxicity, depending on the route of exposure and the species used. Sulfosate is not toxic at low dose oral levels and *via* the inhalation route in rats. In rabbits, sulfosate is not acutely toxic *via* the dermal route, is non-irritating to the skin, but is a severe eye irritant. It produces a weak dermal sensitization reaction in guinea pigs.

In addition, sulfosate is unpalatable in the rodent diet, since in both subchronic and chronic studies in rats and mice, decreased weight gain could be correlated with decreased food consumption with little change in feed efficiency.

There is no indication of an increased susceptibility of fetuses or offspring in rats or rabbits after prenatal and/or postnatal exposure to sulfosate. A similar finding was made with respect to glyphosate, a structurally related pesticide.

There are no data gaps for the assessment of effects of sulfosate following *in utero* exposure or the effects on young animals following early exposure (exception - developmental neurotoxicity).

Sulfosate is classified as a Group E carcinogen, based on the absence of tumorigenicity in

two species of animals in two acceptable studies.

The main difference between sulfosate and glyphosate can best be seen in a comparison of their RfDs. The RfD for glyphosate is 2.0 mg/kg/day and the RfD for sulfosate is 0.10 mg/kg/day [a 20 fold difference]. The enhanced toxicity of sulfosate in comparison to glyphosate is due to the presence of the trimesium cation in the sulfosate molecule.

There are no data gaps for the standard Subdivision F Guideline requirements for a food-use chemical by 40 CFR Part 158, however a developmental neurotoxicity study in the rat is required. This is based on the weight -of-the-evidence for concerns of neurotoxicity in the mouse oncogenicity study, the gavage dog studies, 21-day dermal toxicity study in rats, and acute and subchronic neurotoxicity studies in the rat. Signs of neurotoxicity due to sulfosate included FOB effects in the rat neurotoxicity studies, treatment related salivation and emesis in the dog. There were also concerns for hydrocephalus in all dog studies (at least one dog/study at the high dose, none in controls) and possible treatment related histopathology in the mouse carcinogenicity and 21 day dermal rat studies.

VII. ACUTE TOXICITY

Acute Toxicity of SULPHOSATE

Guideline No.	Study Type	MRID #(S)	Results	Toxicity Category
81-1	Acute Oral	00126608, 00132172	LD50 = 748 mg/kg	III
81-2	Acute Dermal	00126608, 00132173	LD50 = 2000 mg/kg	III
81-3	Acute Inhalation	00126609	LC50 = 6.9 m/L	IV
81-4	Primary Eye Irritation	00126608, 00132172	Slight Irritation	III
81-5	Primary Skin Irritation	00126608, 00132172	0.19/4.00	III
81-6	Dermal Sensitization	00154270	slight sensitizer	

VIII. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOEL= 100 UF = 100	Clinical signs indicative of neurotoxicity including tail flick, landing foot splay, forelimb grip strength, hindlimb grip strength and motor activity.	Acute Neurotoxicity-Rat
	Acute RfD = 1.0 mg/kg		
Chronic Dietary	NOEL = 10 UF = 100	Clinical signs indicative of neurotoxicity (emesis and salivation).	Chronic Toxicity - Dog
	Chronic RfD = 0.10 mg/kg/day		
Short-, Intermediate or Long-Term (Dermal)	**None**	Based on the lack of systemic toxicity at 1000 mg/kg/day (NOEL) with the technical product and minimal sciatic nerve fiber degeneration of unstated severity at 1000 mg/kg/day (LOEL) (NOEL = 250 mg/kg/day) with the formulation in the 21-day dermal toxicity studies, the Committee determined that the potential for risk via the dermal route is low due to low toxicity and at this time the current use patterns (agricultural) do not indicate an exposure concern. **At this time dermal risk assessments are not required.**	
Short Term (Inhalation)[a]	Oral NOEL= 100 MOE = 100	Clinical signs indicative of neurotoxicity including tail flick, landing foot splay, forelimb grip strength, hindlimb grip strength and motor activity.	Acute Neurotoxicity-Rat
Intermediate & Long- Term (Inhalation)[a]	Oral NOEL= 10 MOE = 100	Clinical signs indicative of neurotoxicity (emesis and salivation).	Chronic Toxicity - Dog

a= Since an oral NOEL was selected, an inhalation absorption factor (100%) should be used.

Reference: Vullo, T., E. Korenman, R.P. Mazo, D.G. Gonez, M.D. Deck, and P.T. Cahill. 1997. Diagnosis of cerebral ventriculomegaly in normal adult beagles using quantitative MRI. *Vet. Radiol. Ultrasound*, Jul.-Aug. 38 (4):277-81.

Attachment 2: Report of the FQPA Safety Factor Committee (B. Tarplee and J. Rowland, HED Doc. No. 012681, 6/29/98)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

012681

29-JUNE-1998

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: ***SULFOSATE*** - Report of the FQPA Safety Factor Committee.
This document supercedes the previous FQPA Safety Factor Committee report for Sulfosate.

FROM: Brenda Tarplee, Executive Secretary
FQPA Safety Factor Committee
Health Effects Division (7509C)
and
Jess Rowland, Executive Secretary
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

THROUGH: Ed Zager, Chairman
FQPA Safety Factor Committee
Health Effects Division (7509C)

TO: Steve Knizner, Branch Senior Scientist
Risk Characterization & Analysis Branch
Health Effects Division (7509C)

PC Code: 128501

The Health Effects Division (HED) FQPA Safety Factor Committee met on June 29, 1998 to re-evaluate the hazard and exposure data for Sulfosate and recommend application of the FQPA Safety Factor (as required by Food Quality Protection Act of August 3, 1996), to ensure the protection of infants and children from exposure to this pesticide. The Committee recommended that the 10x Safety Factor for increased susceptibility of infants and children should be reduced to 3x for this pesticide. This document supercedes the previous FQPA Safety Factor Committee report for Sulfosate.

I. HAZARD ASSESSMENT

1. Determination of Susceptibility

The Hazard Identification Assessment Review Committee (HIARC) determined that the data provided no indication of increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to Sulfosate. In the prenatal developmental toxicity studies in rats and rabbits, evidence of developmental toxicity was seen only in the presence of maternal toxicity. In the two-generation reproduction study in rats, effects in the offspring were observed only at treatment level which resulted in evidence of parental toxicity (HIARC Report, dated June 25, 1998; HED Doc. No. 012652.).

2. Adequacy of Toxicity Database

There are **no data gaps** for the assessment of the effects of Sulfosate following *in utero* and/or postnatal exposure according to the Subdivision F Guideline requirements. However, the HIARC has determined that, based on a weight-of-the-evidence of neurotoxicity seen in subchronic and chronic studies **a developmental neurotoxicity study is required for Sulfosate.** For details refer to the Report of the HIARC dated June 25, 1998; HED Doc. No. 012652.

II. EXPOSURE ASSESSMENT

1. Dietary Exposure Considerations

Tolerances for Sulfosate have been established under 40 CFR § 180.489 (a) for bananas, citrus fruit, grapes, stone fruit, and almond hulls. Tolerances with an expiration date of March 9, 1998 have also been established under 40 CFR § 180.489 (b) for corn, soybeans, meat, milk, poultry, and eggs [HED is recommending that these tolerances be made permanent]. Tolerances are also proposed for pome fruit, wheat (grain, straw, forage, hay, and bran), and meat (including liver and meat byproducts) [HED is recommending that these tolerances be established].

Residues of Sulfosate are systemic and likely to transfer to meat, milk, poultry, and eggs. Field trial data indicate that the only human food items with significant residues were soybean seed and wheat grain, both of which had a high frequency of positive findings. Monitoring data are currently not available for Sulfosate.

The HED DRES system was used to assess the risk from dietary exposure to Sulfosate in food. The dietary risk assessment makes the very conservative assumption that all

commodities contain residues of Sulfosate at the level of the tolerance. This will result in an overestimate of dietary exposure.

2. Drinking Water Exposure Considerations

Since monitoring data are not available for drinking water exposure to Sulfosate, preliminary Estimated Environmental Concentrations (EECs) have been calculated for ground and surface water based on the current EFED first level screening models, SCI-GROW and GENEEC respectively.

3. Residential Exposure Considerations

There are currently no registered residential uses for Sulfosate.

III. RISK CHARACTERIZATION

1. Determination of the Factor

The Committee recommended that the **10x factor** for increased susceptibility of infants and children (as required by FQPA) should be **reduced to 3x.**

2. Rationale for Selection of the FQPA Safety Factor

The HIARC determined that the data indicate that there is no increased susceptibility to young rats or rabbits following *in utero* exposure in prenatal studies or in the postnatal study in rats, and the toxicology data base is complete. Additionally, the exposure assessments for Sulfosate do not indicate a concern for potential risk to infants and children since: 1) the dietary exposure assessments are unrefined (assuming that all commodities contain tolerance level residues) resulting in an overestimate of dietary exposure; 2) data from modeling are used for the ground and surface source drinking water exposure assessments, resulting in estimates considered to be reasonable upper-bound concentrations; and 3) there are currently no registered residential uses for Sulfosate.

However, the Committee recommended that the FQPA Safety Factor should not removed, instead it should be reduced to3x because of the concern for the overall neurotoxicity exhibited in long-term studies in adult animals (mice, rats, and dogs). In mice, Sulfosate induced degeneration of the sciatic nerve, lumbar spinal root and lumbar spinal white matter. In rats, degeneration of the sciatic nerve was seen following dermal applications. In dogs, hydrocephalus and/or dilated ventricles were observed following subchronic and chronic exposures. In addition, clinical signs indicative of neurotoxicity such as salivation, tremors, emesis, decreased activity was seen in rats and dogs. Based on these factors, the HIARC determined that a developmental neurotoxicity study in rats is required to characterize the observed neuropathology in the subchronic and chronic

studies. The FQPA Safety Committee concurred with the HIARC and thus determined the need for a 3x Safety Factor.

3. Identification of Population Subgroup

The Committee determined that the FQPA Safety Factor (3x) factor is applicable for the following subpopulations:

Acute Dietary: All populations which include Infants and Children. The FQPA factor is appropriate for these populations because the endpoint is based on effects observed after a single dose in the Acute Neurotoxicity Study in Rats and also because of the need for a developmental neurotoxicity study in rats.

Chronic Dietary: All populations which include Infants and Children. The FQPA factor is appropriate for these populations because the endpoint is based on clinical signs indicative of neurotoxicity (emesis and salivation) in the One-Year Chronic Dog study and also because of the need for a developmental neurotoxicity study in rats.

FQPA Safety Factor Committee Meeting
29-JUNE-1998
Chemical: Sulfosate - Revisit

Name	Division/Branch
Jess Rowlar	HED/SAB.
Debbie McCall	RD
Donald STUBBS	RD
Jim Tompkins.	RD
Juliania CRUZ	HED/RAB-1
Jim Carleton	EFED
Daniel Rieder	EFED
[illegible]	HED
Ed Zager	HED
Brenda Tarplee	HED/RAB1
Kathy Monk	SRRD
Rick Keigwin	RD
George Kramer	HED

Attachment 3: International Residue Limit Status

INTERNATIONAL RESIDUE LIMIT STATUS

Chemical Name:	Common Name:	X Proposed tolerance □ Reevaluated tolerance □ Other	Date:
sulfonium, trimethyl-salt with N-(phosphono-methyl) glycine (1:1)	Sulfosate		04/16/99

Codex Status (Maximum Residue Limits)	U. S. Tolerances
X No Codex proposal step 6 or above □ No Codex proposal step 6 or above for the crops requested	Petition Number:7F04854 DP Barcode:D243318 Other Identifier:
Residue definition: N/A	Reviewer/Branch: G.F. Kramer
	Residue definition: parent ions

Crop (s)	MRL (mg/kg)	Crop(s)	Tolerance (ppm)
		Soybean, seed	21
		Soybean, hulls	45
		Aspirated grain fractions	1300
		Cattle, goat, hog, sheep, and horse kidney	6.0
		Cattle, goat, hog, sheep, and horse meat byproducts (exc. kidney)	1.5
		Cattle, goat, hog, sheep, and horse meat	1.0
		Cattle, goat, hog, sheep, and horse fat	0.5
		Milk	1.5
		Eggs	0.05

Limits for Canada	Limits for Mexico
X No Limits □ No Limits for the crops requested	X No Limits □ No Limits for the crops requested
Residue definition:	Residue definition:

Crop(s)	MRL (mg/kg)	Crop(s)	MRL (mg/kg)
Notes/Special Instructions:.			

Rev 1998

Attachment 4: Glyphosate-trimesium (sulfosate) - Dietary Exposure Analysis for Sulfosate. (S. Chun, 4/22/99, DP Barcode 254804)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: April 22, 1999

SUBJECT: Glyphosate-trimesium (Sulfosate) - Dietary Exposure Analysis for Sulfosate. Chemical#: 128501. DP Barcode: D254804. Case #: 289000. Submission #: S526352.

FROM: Susie Chun, Chemist
Registration Action Branch 1
Health Effects Division

THROUGH: Felecia Fort, Chemist
Douglas Dotson, Chemist
Dietary Exposure Science Advisory Council

Melba Morrow, D.V.M., Branch Senior Scientist
Registration Action Branch 1
Health Effects Division

TO: Jessica Kidwell, Toxicologist
Registration Action Branch 1
Health Effects Division

Action Requested

Provide an estimate of the dietary exposure and associated risks for trimethyl-salt with N-(phosphonomethyl)glycine (1:1) [or sulfosate] resulting from an amended use request in/on soybean RACs (7F4854). The amended use will also affect expired tolerances for residues in meat and milk and proposed tolerances for poultry and eggs.

The following are the proposed tolerances as a result of the amended use:

Soybean, seed	21 ppm
Kidney*	6.0 ppm
Meat Byproducts* (except kidney)	1.5 ppm
Meat*	1.0 ppm
Fat*	0.5 ppm
Milk	1.5 ppm

Poultry Meat Byproducts	0.1 ppm
Poultry Meat	0.05 ppm
Poultry Fat	0.05 ppm
Eggs	0.05 ppm

* of cattle, hogs, sheep, goats, and horses

Executive Summary

For the acute dietary analysis, an acute Population Adjusted Dose (aPAD) of 0.333 mg/kg/day (incorporating 10x for interspecies extrapolation, 10x for intraspecies extrapolation, and 3x FQPA Safety Factor) was used. The Tier 1 acute dietary analysis for sulfosate is a highly conservative estimate of dietary exposure with the use of tolerance level residue values and 100 percent crop treated (CT). The percent aPADs were below HED's level of concern at the 95th percentile for the U.S. population and all subgroups. The results of this analysis indicate that the acute dietary risk associated with the amended use of sulfosate on soybeans is below the Agency's level of concern.

For the chronic dietary analysis, a chronic Populations Adjusted Dose (cPAD) of 0.0333 mg/kg/day (incorporating 10x for interspecies extrapolation, 10x for intraspecies extrapolation, and 3x FQPA Safety Factor) was used. The Tier 3 chronic dietary analysis for sulfosate is a more refined estimate with the use of some anticipated residues (ARs) and %CT information. Percent CT information was used for oranges, grapefruit, soybeans, corn, peaches, and wheat. Crops (wheat, corn, and peaches) that the Biological and Economics Analysis Division (BEAD) had estimated at 0 % CT were rounded up to 1 % CT. However, it still is a high over-estimation of dietary exposure, since tolerance level residue values were used for the majority of the commodities. Further refinements would entail the use of ARs and/or monitoring data for all commodities. The percent cPADs were below HED's level of concern for the U.S. population and all subgroups. The results of this analysis indicate that the chronic dietary risk associated with the amended use of sulfosate on soybeans is below the Agency's level of concern.

Toxicological Endpoints

On June 12, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) met to re-examine the neurotoxicity hazard assessment/characterization for sulfosate. This was a follow-up to the HIARC meeting held on April 26, 1998, which met to re-assess the Reference Dose (RfD) established in 1994 and select the toxicological endpoints for acute dietary as well as occupational exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to sulfosate as required by the Food Quality Protection Act (FQPA) of 1996.

The doses and toxicological endpoints selected for various exposure scenarios are summarized in Table 1 (Memo, W. Dykstra and J. Rowland, HED Doc. No. 125594, 4/23/98; Memo, M. Copley and J. Rowland, HED Doc. No. 012652, 6/25/98).

Table 1. Summary of Toxicological Endpoints for Sulfosate Use in Human Risk Assessment

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOAEL= 100 UF = 100 FQPA SF= 3	Clinical signs indicative of neurotoxicity including tail flick, landing foot splay, forelimb grip strength, hindlimb grip strength and motor activity.	Acute Neurotoxicity-Rat
	Acute RfD = 1.0 mg/kg/day **Acute PAD** = 0.333 mg/kg/day		
Chronic Dietary	NOAEL = 10 UF = 100 FQPA SF = 3	Clinical signs indicative of neurotoxicity (emesis and salivation).	Chronic Toxicity - Dog
	Chronic RfD = 0.10 mg/kg/day **Chronic PAD** = 0.0333 mg/kg/day		

Cancer

Based on the lack of evidence of carcinogenicity in mice (MRIDs 40214006, 41209907) and rats (MRIDs 40214007, 41209905, 41209907) at doses that were judged to be adequate to assess the carcinogenic potential, Sulfosate was classified as a **"Group E"** chemical - no evidence for carcinogenicity in humans - based on the *"Guidelines for Carcinogen Risk Assessment" [FR51: 33992-34003, 1986]* for classifying the weight-of-evidence for carcinogenicity. (RfD report - 26-JUL-1994).

FQPA Recommendation

Based upon a weight of evidence consideration , the HIARC decided **to require the conduct of a developmental neurotoxicity study with sulfosate** to evaluate the potential for effects on functional development (Memo, M. Copley and J. Rowland, HED Doc. No. 012652, 6/25/98).

The FQPA Safety Factor Committee (SFC) recommended that the **10x factor** for increased susceptibility of infants and children (as required by FQPA) be **reduced to 3x** because of the concern for the overall neurotoxicity exhibited in long-term studies in adult animals (mice, rats, and dogs). The HIARC determined that a developmental neurotoxicity study in rats is required to characterize the observed neuropathology in the subchronic and chronic studies. The FQPA SFC concurred with the HIARC and thus determined the need for a 3x Safety Factor (Memo, B. Tarplee, HED DOC. NO. 01268, 6/29/98).

The Committee determined that the FQPA SF of 3x is applicable for the following subpopulations:

Acute Dietary: All populations which include Infants and Children. The FQPA factor is appropriate for these populations because the endpoint is based on effects observed after a single dose in the Acute Neurotoxicity Study in Rats and also because of the need for a developmental neurotoxicity study in rats. This will result in an acute population adjusted dose (aPAD) of 0.333 mg/kg/day.

Chronic Dietary: All populations which include Infants and Children. The FQPA factor is appropriate for these populations because the endpoint is based on clinical signs indicative of neurotoxicity (emesis and salivation) in the One-Year Chronic Dog study and also because of the need for a developmental neurotoxicity study in rats. This will result in a chronic population adjusted dose (cPAD) of 0.0333 mg/kg/day.

Residue Information

Tolerances, including time-limited, for sulfosate are published in 40 CFR §180.489.

For the acute dietary analysis, tolerance level residues, 100% CT, and an aPAD of 0.333 mg/kg/day were used.

For the chronic dietary analysis, tolerance level residues, anticipated residue levels for soybean RACs based on field trial data (Memo, G. Kramer, D243318, in preparation), % CT information provided by BEAD [S. Smearman, 4/14/99], and cPAD of 0.0333 mg/kg/day were used. Percent CT information was used for oranges, grapefruit, corn, peaches, and wheat. Crops that BEAD had estimated at 0 % CT (wheat, corn, and peaches) were rounded up to 1 % CT. The registrant submitted a projected market share percent of 20% for soybeans. BEAD has concurred with this value (higher than the 2% in the BEAD quantitative usage data) [personal communication to J. Kidwell from S. Smeraman, 4/21/99]. Therefore, 20% was used in the chronic dietary analysis for soybeans.

A dietary analysis for acute and chronic with the Dietary Risk Evaluation System (DRES) system was previously completed (Memo, B. Steinwand, 2/16/96).

Results

The Dietary Exposure Evaluation Model (DEEM™) analysis evaluated the individual food consumption as reported by respondents in the USDA 1989-91 Continuing Surveys for Food Intake by Individuals (CSFII) and accumulated exposure to the chemical for each commodity. Summaries of the residue information used in the acute and chronic and cancer dietary exposure analyses are attached (Attachments 1 and 3).

Acute Dietary Exposure Analysis

The acute dietary exposure analysis estimates the distribution of single-day exposures for the U.S. population and certain subgroups and accumulates exposure to the chemical for each commodity. Each analysis assumes uniform distribution of sulfosate for the commodities on which sulfosate is used.

The FQPA SFC reduced the 10x to a factor of 3x resulting in an aPAD of 0.333 mg/kg/day. HED's level of concern is for acute dietary exposures greater than 100% aPAD. The acute dietary exposure analysis was performed for the U.S. population and 27 subgroups. A summary with all population subgroups is attached (Attachment 2).

Dietary exposures and associated acute risk at the 95th percentile are shown in Table 1. Besides the U.S. population, the subgroups included in Table 1 represent the highest dietary exposures for their respective subgroups (i.e., children, females , and also the other general population subgroup higher than U.S. population).

Table 1. - Acute Dietary Exposure Results

Subgroups	Exposure (mg/kg/day)	% aPAD
U.S. Population	0.033377	10
Non-hispanic blacks	0.037008	11
All infants (< 1 year)	0.140195	42
Females(13-19 yrs/np/nn)	0.024913	8

Chronic Dietary Analysis

The chronic DEEM™ dietary exposure analysis used mean consumption (3 day average). The FQPA SFC reduced the 10x to a factor of 3x resulting in cPAD of 0.0333 mg/kg/day. HED's level of concern is for chronic dietary exposures greater than 100% cPAD (33.3% RfD). Dietary exposures for the U.S. general population and other subgroups are presented in Table 2. The other subgroups included in Table 2 represent the highest dietary exposures for their respective subgroups (i.e., children, females, and also the other general population subgroup higher than U.S. population).

Table 2. - Chronic Dietary Exposure Results

Subgroups	Exposure (mg/kg/day)	% cPAD
U.S. Population (48 states)	0.003078	9
Hispanics	0.003346	10
Children(1 - 6 years old)	0.008682	26
Females (13-19, np/nn)	0.002643	8

The complete chronic dietary exposure analysis is attached (Attachment 4).

Conclusions

The Tier 1 acute dietary analysis for sulfosate is a highly conservative estimate of dietary exposure with the use of tolerance level residue values and 100 percent of the commodities assumed to be treated. The percent aPADs were below HED's level of concern at the 95th

percentile for the U.S. population and all subgroups with the highest exposure of 42% aPAD in the subgroup all infants (< 1 year). The results of this analysis indicate that the acute dietary risk associated with the amended use of sulfosate on soybeans is below the Agency's level of concern.

The Tier 3 chronic dietary analysis for sulfosate is a more refined estimate with the use of some ARs and %CT information. However, it still is a high over-estimation of dietary exposure, since tolerance level residue values were used for the majority of the commodities. Further refinements would entail the use of ARs and/or monitoring data for all commodities. The percent cPADs were below HED's level of concern for the U.S. population and all subgroups with the highest exposure of 26% cPAD in the subgroup children (1-6 years old). The results of this analysis indicate that the chronic dietary risk associated with the amended use of sulfosate on soybeans is below the Agency's level of concern.

Attachment 1: Residue File -Acute
Attachment 2: Acute DEEM™ analysis - U.S. Population (S. Chun, 4/15/99)
Attachment 3: Residue File - Chronic
Attachment 4: Chronic DEEM™ analysis (S. Chun, 4/21/99)

cc(with attachments): S. Chun (RAB1); M. Sahafeyan (CEB1), PP# 7F4854
RDI: Dietary Exposure SAC [F. Fort (4/19/99), D. Dotson 4/19/99)]
S. Chun:806R:CM#2:(703)305-2249:7509C:RAB1

Attachment 1: Residue Information - Acute

Filename: C:\DEEM\resdata\128501a.R96

Chemical name: Sulfosate

RfD(Chronic): .0333 mg/kg bw/day NOEL(Chronic): .1 mg/kg bw/day

RfD(Acute): .333 mg/kg bw/day NOEL(Acute): 1 mg/kg bw/day

Date created/last modified: 04-15-1999/08:16:57/8 Program ver. 6.73

Comment: aPAD of 0.333 mg/kg/d and c PAD of 0.0333 mg/kg/d includes (10x inter, 10x intra, 3x FQPA)

Food Code	Crop Grp	Food Name	RESIDUE (ppm)	RDF #	Adj.Factors #1	Adj.Factors #2	Comment
72	O	Bananas	0.050000	0	1.000	1.000	P, 4F4343
73	O	Bananas-dried	0.050000	0	3.900	1.000	P, 4F4343
378	O	Bananas-juice	0.050000	0	1.000	1.000	P, 4F4343
13	O	Grapes	0.100000	0	1.000	1.000	P, 1F3950
15	O	Grapes-juice	0.100000	0	1.200	1.000	P, 1F3950
392	O	Grapes-juice-concentrate	0.100000	0	3.600	1.000	P, 1F3950
195	O	Grapes-leaves	0.100000	0	1.000	1.000	P, 1F3950
14	O	Grapes-raisins	0.200000	0	1.000	1.000	P, 1F3950
315	O	Grapes-wine and sherry	0.100000	0	1.000	1.000	P, 1F3950
480	O	Plantains-green	0.050000	0	1.000	1.000	P, 4F4343
94	O	Plantains-ripe	0.050000	0	1.000	1.000	P, 4F4343
481	O	Plantains-dried	0.050000	0	3.900	1.000	P, 4F4343
482	O	Soybeans-protein isolate	21.000000	0	1.000	1.000	New, 3 ppm + 18 ppm, 7F04854
323	M	Beef-dried	1.000000	0	1.920	1.000	New, 7F4854, 0.4 ppm + 0.6 ppm
324	M	Beef-fat w/o bones	0.500000	0	1.000	1.000	New, 7F4854, 0.2 ppm + 0.3 ppm
325	M	Beef-kidney	6.000000	0	1.000	1.000	New, 7F4854, 3.5 ppm + 2.5 ppm
327	M	Beef-lean (fat/free) w/o bones	1.000000	0	1.000	1.000	New, 7F4854, 0.4 ppm + 0.6 ppm
326	M	Beef-liver	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
321	M	Beef-meat byproducts	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
322	M	Beef-other organ meats	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
330	M	Goat-fat w/o bone	0.500000	0	1.000	1.000	New, 7F4854, 0.2 ppm + 0.3 ppm
331	M	Goat-kidney	6.000000	0	1.000	1.000	New, 7F4854, 3.5 ppm + 2.5 ppm
333	M	Goat-lean (fat/free) w/o bone	1.000000	0	1.000	1.000	New, 7F4854, 0.4 ppm + 0.6 ppm
332	M	Goat-liver	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
328	M	Goat-meat byproducts	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
329	M	Goat-other organ meats	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
334	M	Horsemeat	1.000000	0	1.000	1.000	New, 7F4854, 0.4 ppm + 0.6 ppm
344	M	Pork-fat w/o bone	0.500000	0	1.000	1.000	New, 7F4854, 0.2 ppm + 0.3 ppm
345	M	Pork-kidney	6.000000	0	1.000	1.000	New, 7F4854, 3.5 ppm + 2.5 ppm
347	M	Pork-lean (fat free) w/o bone	1.000000	0	1.000	1.000	New, 7F4854, 0.4 ppm + 0.6 ppm
346	M	Pork-liver	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm

342	M	Pork-meat byproducts	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
343	M	Pork-other organ meats	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
338	M	Sheep-fat w/o bone	0.500000	0	1.000	1.000	New, 7F4854, 0.2 ppm + 0.3 ppm
339	M	Sheep-kidney	6.000000	0	1.000	1.000	New, 7F4854, 3.5 ppm + 2.5 ppm
341	M	Sheep-lean (fat free) w/o bone	1.000000	0	1.000	1.000	New, 7F4854, 0.4 ppm + 0.6 ppm
340	M	Sheep-liver	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
336	M	Sheep-meat byproducts	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
337	M	Sheep-other organ meats	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
429	M	Veal-dried	1.000000	0	1.920	1.000	New, 7F4854, 0.4 ppm + 0.6 ppm
424	M	Veal-fat w/o bones	0.500000	0	1.000	1.000	New, 7F4854, 0.2 ppm + 0.3 ppm
426	M	Veal-kidney	6.000000	0	1.000	1.000	New, 7F4854, 3.5 ppm + 2.5 ppm
425	M	Veal-lean (fat free) w/o bones	1.000000	0	1.000	1.000	New, 7F4854, 0.4 ppm + 0.6 ppm
427	M	Veal-liver	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
430	M	Veal-meat byproducts	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
428	M	Veal-other organ meats	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
366	P	Chicken-byproducts	0.100000	0	1.000	1.000	New, 7F4854
368	P	Chicken-fat w/o bones	0.050000	0	1.000	1.000	New, 7F4854
367	P	Chicken-giblets(liver)	0.050000	0	1.000	1.000	New, 7F4854
385	P	Chicken-giblets (excl. liver)	0.100000	0	1.000	1.000	New, 7F4854
369	P	Chicken-lean/fat free w/o bones	0.050000	0	1.000	1.000	New, 7F4854
364	P	Eggs-white only	0.050000	0	1.000	1.000	P, 3F4238, 0.02 ppm + 0.03 ppm
363	P	Eggs-whole	0.050000	0	1.000	1.000	P, 3F4238, 0.02 ppm + 0.03 ppm
365	P	Eggs-yolk only	0.050000	0	1.000	1.000	P, 3F4238, 0.02 ppm + 0.03 ppm
362	P	Poultry-other-fat w/o bones	0.050000	0	1.000	1.000	New, 7F4854
361	P	Poultry-other-giblets(liver)	0.050000	0	1.000	1.000	New, 7F4854
360	P	Poultry-other-lean (fat free) w/	0.050000	0	1.000	1.000	New, 7F4854
355	P	Turkey-byproducts	0.100000	0	1.000	1.000	New, 7F4854
357	P	Turkey--fat w/o bones	0.050000	0	1.000	1.000	New, 7F4854
356	P	Turkey-giblets (liver)	0.050000	0	1.000	1.000	New, 7F4854
358	P	Turkey- lean/fat free w/o bones	0.050000	0	1.000	1.000	New, 7F4854
449	P	Turkey-other organ meats	0.100000	0	1.000	1.000	New, 7F4854
398	D	Milk-based water	0.200000	0	1.000	1.000	P
319	D	Milk-fat solids	0.200000	0	1.000	1.000	P
318	D	Milk-nonfat solids	0.200000	0	1.000	1.000	P
320	D	Milk sugar (lactose)	0.200000	0	1.000	1.000	P
303	6A	Soybean-other	21.000000	0	1.000	1.000	New, 3 ppm + 18 ppm, 7F04854
307	6A	Soybeans-flour (defatted)	21.000000	0	1.000	1.000	New, 3 ppm + 18 ppm, 7F04854
306	6A	Soybeans-flour (low fat)	21.000000	0	1.000	1.000	New, 3 ppm + 18 ppm, 7F04854
305	6A	Soybeans-flour (full fat)	21.000000	0	1.000	1.000	New, 3 ppm + 18 ppm, 7F04854
304	6A	Soybeans-mature seeds dry	21.000000	0	1.000	1.000	New, 3 ppm + 18 ppm, 7F04854
297	6A	Soybeans-oil	21.000000	0	1.000	1.000	New, 3 ppm + 18 ppm, 7F04854
255	6A	Soybeans-sprouted seeds	21.000000	0	0.330	1.000	New, 3 ppm + 18 ppm, 7F04854
20	10	Citrus citron	0.050000	0	1.000	1.000	0F3890

23	10	Grapefruit-juice	0.050000	0	2.100	1.000	0F3890
441	10	Grapefruit-juice-concentrate	0.050000	0	8.260	1.000	0F3890
448	10	Grapefruit peel	0.050000	0	1.000	1.000	0F3890
22	10	Grapefruit-peeled fruit	0.050000	0	1.000	1.000	0F3890
24	10	Kumquats	0.050000	0	1.000	1.000	0F3890
28	10	Lemons-juice	0.050000	0	2.000	1.000	0F3890
442	10	Lemons-juice-concentrate	0.050000	0	11.400	1.000	0F3890
27	10	Lemons-peel	0.050000	0	1.000	1.000	0F3890
26	10	Lemons-peeled fruit	0.050000	0	1.000	1.000	0F3890
32	10	Limes-juice	0.050000	0	2.000	1.000	0F3890
443	10	Limes-juice-concentrate	0.050000	0	6.000	1.000	0F3890
31	10	Limes-peel	0.050000	0	1.000	1.000	0F3890
30	10	Limes-peeled fruit	0.050000	0	1.000	1.000	0F3890
36	10	Oranges-juice	0.050000	0	1.800	1.000	0F3890
33	10	Oranges-juice-concentrate	0.050000	0	6.700	1.000	0F3890
35	10	Oranges-peel	0.050000	0	1.000	1.000	0F3890
34	10	Oranges-peeled fruit	0.050000	0	1.000	1.000	0F3890
37	10	Tangelos	0.050000	0	1.000	1.000	0F3890
38	10	Tangerines	0.050000	0	1.000	1.000	0F3890
39	10	Tangerines-juice	0.050000	0	2.300	1.000	0F3890
420	10	Tangerines-juice-concentrate	0.050000	0	7.350	1.000	0F3890
52	11	Apples	0.050000	0	1.000	1.000	Pend, 0F04554
53	11	Apples-dried	0.050000	0	8.000	1.000	Pend, 0F04554
54	11	Apples-juice/cider	0.050000	0	1.300	1.000	Pend, 0F04554
377	11	Apples-juice-concentrate	0.050000	0	3.900	1.000	Pend, 0F04554
55	11	Crabapples	0.050000	0	1.000	1.000	Pend, 0F04554
81	11	Loquats	0.050000	0	1.000	1.000	Pend, 0F04554
56	11	Pears	0.050000	0	1.000	1.000	Pend, 0F04554
57	11	Pears-dried	0.050000	0	6.250	1.000	Pend, 0F04554
404	11	Pears-juice	0.050000	0	1.000	1.000	Pend, 0F04554
58	11	Quinces	0.050000	0	1.000	1.000	Pend, 0F04554
410	12	Apricot juice	0.050000	0	1.000	1.000	P, 3F4238
59	12	Apricots	0.050000	0	1.000	1.000	P, 3F4238
60	12	Apricots-dried	0.050000	0	6.000	1.000	P, 3F4238
61	12	Cherries	0.050000	0	1.000	1.000	P, 3F4238
62	12	Cherries-dried	0.050000	0	4.000	1.000	P, 3F4238
63	12	Cherries-juice	0.050000	0	1.500	1.000	P, 3F4238
64	12	Nectarines	0.050000	0	1.000	1.000	P, 3F4238
65	12	Peaches	0.050000	0	1.000	1.000	P, 3F4238
66	12	Peaches-dried	0.050000	0	7.000	1.000	P, 3F4238
402	12	Peaches-juice	0.050000	0	1.000	1.000	P, 3F4238
67	12	Plums (damsons)	0.050000	0	1.000	1.000	P, 3F4238
68	12	Plums-prunes (dried)	0.200000	0	1.000	1.000	P, 3F4238

69	12	Plums/prune-juice	0.200000	0	1.000	1.000	P, 3F4238
40	14	Almonds	0.050000	0	1.000	1.000	P, 4F4343
51	14	Beechnuts	0.050000	0	1.000	1.000	P, 4F4343
41	14	Brazil nuts	0.050000	0	1.000	1.000	P, 4F4343
49	14	Butter nuts	0.050000	0	1.000	1.000	P, 4F4343
42	14	Cashews	0.050000	0	1.000	1.000	P, 4F4343
43	14	Chestnuts	0.050000	0	1.000	1.000	P, 4F4343
44	14	Filberts (hazelnuts)	0.050000	0	1.000	1.000	P, 4F4343
45	14	Hickory nuts	0.050000	0	1.000	1.000	P, 4F4343
46	14	Macadamia nuts (bush nuts)	0.050000	0	1.000	1.000	P, 4F4343
47	14	Pecans	0.050000	0	1.000	1.000	P, 4F4343
431	14	Walnut oil	0.050000	0	1.000	1.000	P, 4F4343
48	14	Walnuts	0.050000	0	1.000	1.000	P, 4F4343
267	15	Corn grain-bran	0.200000	0	1.000	1.000	P
266	15	Corn grain-endosperm	0.200000	0	1.000	1.000	P
289	15	Corn grain-oil	0.200000	0	1.000	1.000	P
268	15	Corn grain/sugar/hfcs	0.200000	0	1.500	1.000	P
388	15	Corn grain/sugar-molasses	0.200000	0	1.500	1.000	P
237	15	Corn/pop	0.200000	0	1.000	1.000	P
278	15	Wheat-bran	2.500000	0	1.000	1.000	Pend, 0F04554
279	15	Wheat-flour	0.750000	0	1.000	1.000	Pend, 0F04554
277	15	Wheat-germ	0.750000	0	1.000	1.000	Pend, 0F04554
437	15	Wheat-germ oil	0.750000	0	1.000	1.000	Pend, 0F04554
276	15	Wheat-rough	0.750000	0	1.000	1.000	Pend, 0F04554

Attachment 2: Acute Dietary Exposure Analysis

U.S. Environmental Protection Agency Ver. 6.73
DEEM ACUTE analysis for SULFOSATE (1989-92 data)
Residue file: 128501a.R96 Adjustment factor #2 NOT used.
Analysis Date: 04-15-1999/08:30:20• Residue file dated: 04-15-1999/08:23:12/8
Acute Reference Dose (aRfD) = 0.333000 mg/kg body-wt/day
NOEL (Acute) = 1.000000 mg/kg body-wt/day
Run Comment: aPAD of 0.333 mg/kg/d and c PAD of 0.0333 mg/kg/d includes (10x inter, 10x intra, 3x FQPA)

Summary calculations:

	95th Percentile			99th Percentile			99.9th Percentile		
	Exposure	% aRfD	MOE	Exposure	% aRfD	MOE	Exposure	% aRfD	MOE
U.S. pop - all seasons:	0.033377	10.02	29	0.057111	17.15	17	0.127857	38.40	7
U.S. pop - spring season:	0.032325	9.71	30	0.063776	19.15	15	0.125967	37.83	7
U.S. pop - summer season:	0.033068	9.93	30	0.055880	16.78	17	0.121177	36.39	8
U.S. pop - autumn season:	0.035624	10.70	28	0.059251	17.79	16	0.125077	37.56	7
U.S. pop - winter season:	0.031649	9.50	31	0.052369	15.73	19	0.129267	38.82	7
Northeast region:	0.034324	10.31	29	0.062264	18.70	16	0.118185	35.49	8
Midwest region:	0.034561	10.38	28	0.058160	17.47	17	0.140164	42.09	7
Southern region:	0.032738	9.83	30	0.053145	15.96	18	0.114972	34.53	8
Western region:	0.032150	9.65	31	0.057112	17.15	17	0.128262	38.52	7
Hispanics:	0.032034	9.62	31	0.083556	25.09	11	0.136610	41.02	7
Non-hispanic whites:	0.032970	9.90	30	0.055267	16.60	18	0.123805	37.18	8
Non-hispanic blacks:	0.037008	11.11	27	0.060809	18.26	16	0.131372	39.45	7
Non-hispanic other:	0.032793	9.85	30	0.056605	17.00	17	0.113411	34.06	8
All infants (<1 year):	0.140195	42.10	7	0.176273	52.93	5	0.265680	79.78	3
Nursing infants (<1 year):	0.050470	15.16	19	0.072385	21.74	13	0.089052	26.74	11
Non-nursing infants (<1 yr):	0.137996	41.44	7	0.202446	60.79	4	0.273748	82.21	3
Children (1-6 years):	0.052023	15.62	19	0.074728	22.44	13	0.115869	34.80	8
Children (7-12 years):	0.039610	11.89	25	0.052848	15.87	18	0.079325	23.82	12
Females (13+/preg/not nsg):	0.020498	6.16	48	0.025702	7.72	38	0.033308	10.00	30
Females (13+/nursing):	0.024435	7.34	40	0.031291	9.40	31	0.047989	14.41	20
Females (13-19 yrs/np/nn):	0.024913	7.48	40	0.033226	9.98	30	0.071516	21.48	13
Females (20+ years/np/nn):	0.019853	5.96	50	0.029068	8.73	34	0.059467	17.86	16
Females (13-50 years):	0.021851	6.56	45	0.031167	9.36	32	0.062985	18.91	15
Males (13-19 years):	0.030972	9.30	32	0.044490	13.36	22	0.103757	31.16	9
Males (20+ years):	0.021829	6.56	45	0.031793	9.55	31	0.044206	13.28	22
Seniors (55+):	0.018479	5.55	54	0.026993	8.11	37	0.038163	11.46	26
Pacific Region:	0.031581	9.48	31	0.054648	16.41	18	0.113787	34.17	8

Attachment 3: Residue Information - Chronic

Filename: C:\DEEM\resdata\128501c.R96
Chemical name: Sulfosate
RfD(Chronic): .0333 mg/kg bw/day NOEL(Chronic): .1 mg/kg bw/day
RfD(Acute): .333 mg/kg bw/day NOEL(Acute): 1 mg/kg bw/day
Date created/last modified: 04-15-1999/08:21:38/8 Program ver. 6.73
Comment: aPAD of 0.333 mg/kg/d and c PAD of 0.0333 mg/kg/d includes (10x inter, 10x intra, 3x FQPA)
Comment: ARs used

Food Code	Crop Grp	Food Name	RESIDUE (ppm)	RDF #	Adj.Factors #1	#2	Comment
72	O	Bananas	0.050000	0	1.000	1.000	P, 4F4343
73	O	Bananas-dried	0.050000	0	3.900	1.000	P, 4F4343
378	O	Bananas-juice	0.050000	0	1.000	1.000	P, 4F4343
13	O	Grapes	0.100000	0	1.000	1.000	P, 1F3950
15	O	Grapes-juice	0.100000	0	1.200	1.000	P, 1F3950
392	O	Grapes-juice-concentrate	0.100000	0	3.600	1.000	P, 1F3950
195	O	Grapes-leaves	0.100000	0	1.000	1.000	P, 1F3950
14	O	Grapes-raisins	0.200000	0	1.000	1.000	P, 1F3950
315	O	Grapes-wine and sherry	0.100000	0	1.000	1.000	P, 1F3950
480	O	Plantains-green	0.050000	0	1.000	1.000	P, 4F4343
94	O	Plantains-ripe	0.050000	0	1.000	1.000	P, 4F4343
481	O	Plantains-dried	0.050000	0	3.900	1.000	P, 4F4343
482	O	Soybeans-protein isolate	1.900000	0	1.000	0.020	New, 3 ppm + 18 ppm, 7F04854, AR
323	M	Beef-dried	1.000000	0	1.920	1.000	New, 7F4854, 0.4 ppm + 0.6 ppm
324	M	Beef-fat w/o bones	0.500000	0	1.000	1.000	New, 7F4854, 0.2 ppm + 0.3 ppm
325	M	Beef-kidney	6.000000	0	1.000	1.000	New, 7F4854, 3.5 ppm + 2.5 ppm
327	M	Beef-lean (fat/free) w/o bones	1.000000	0	1.000	1.000	New, 7F4854, 0.4 ppm + 0.6 ppm
326	M	Beef-liver	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
321	M	Beef-meat byproducts	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
322	M	Beef-other organ meats	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
330	M	Goat-fat w/o bone	0.500000	0	1.000	1.000	New, 7F4854, 0.2 ppm + 0.3 ppm
331	M	Goat-kidney	6.000000	0	1.000	1.000	New, 7F4854, 3.5 ppm + 2.5 ppm
333	M	Goat-lean (fat/free) w/o bone	1.000000	0	1.000	1.000	New, 7F4854, 0.4 ppm + 0.6 ppm
332	M	Goat-liver	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
328	M	Goat-meat byproducts	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
329	M	Goat-other organ meats	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
334	M	Horsemeat	1.000000	0	1.000	1.000	New, 7F4854, 0.4 ppm + 0.6 ppm
344	M	Pork-fat w/o bone	0.500000	0	1.000	1.000	New, 7F4854, 0.2 ppm + 0.3 ppm
345	M	Pork-kidney	6.000000	0	1.000	1.000	New, 7F4854, 3.5 ppm + 2.5 ppm
347	M	Pork-lean (fat free) w/o bone	1.000000	0	1.000	1.000	New, 7F4854, 0.4 ppm + 0.6 ppm
346	M	Pork-liver	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
342	M	Pork-meat byproducts	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm

343	M	Pork-other organ meats	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
338	M	Sheep-fat w/o bone	0.500000	0	1.000	1.000	New, 7F4854, 0.2 ppm + 0.3 ppm
339	M	Sheep-kidney	6.000000	0	1.000	1.000	New, 7F4854, 3.5 ppm + 2.5 ppm
341	M	Sheep-lean (fat free) w/o bone	1.000000	0	1.000	1.000	New, 7F4854, 0.4 ppm + 0.6 ppm
340	M	Sheep-liver	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
336	M	Sheep-meat byproducts	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
337	M	Sheep-other organ meats	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
429	M	Veal-dried	1.000000	0	1.920	1.000	New, 7F4854, 0.4 ppm + 0.6 ppm
424	M	Veal-fat w/o bones	0.500000	0	1.000	1.000	New, 7F4854, 0.2 ppm + 0.3 ppm
426	M	Veal-kidney	6.000000	0	1.000	1.000	New, 7F4854, 3.5 ppm + 2.5 ppm
425	M	Veal-lean (fat free) w/o bones	1.000000	0	1.000	1.000	New, 7F4854, 0.4 ppm + 0.6 ppm
427	M	Veal-liver	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
430	M	Veal-meat byproducts	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
428	M	Veal-other organ meats	1.500000	0	1.000	1.000	New, 7F4854, 0.5 ppm + 1.0 ppm
366	P	Chicken-byproducts	0.100000	0	1.000	1.000	New, 7F4854
368	P	Chicken-fat w/o bones	0.050000	0	1.000	1.000	New, 7F4854
367	P	Chicken-giblets(liver)	0.050000	0	1.000	1.000	New, 7F4854
385	P	Chicken-giblets (excl. liver)	0.100000	0	1.000	1.000	New, 7F4854
369	P	Chicken-lean/fat free w/o bones	0.050000	0	1.000	1.000	New, 7F4854
364	P	Eggs-white only	0.050000	0	1.000	1.000	P, 3F4238, 0.02 ppm + 0.03 ppm
363	P	Eggs-whole	0.050000	0	1.000	1.000	P, 3F4238, 0.02 ppm + 0.03 ppm
365	P	Eggs-yolk only	0.050000	0	1.000	1.000	P, 3F4238, 0.02 ppm + 0.03 ppm
362	P	Poultry-other-fat w/o bones	0.050000	0	1.000	1.000	New, 7F4854
361	P	Poultry-other-giblets(liver)	0.050000	0	1.000	1.000	New, 7F4854
360	P	Poultry-other-lean (fat free) w/	0.050000	0	1.000	1.000	New, 7F4854
355	P	Turkey-byproducts	0.100000	0	1.000	1.000	New, 7F4854
357	P	Turkey--fat w/o bones	0.050000	0	1.000	1.000	New, 7F4854
356	P	Turkey-giblets (liver)	0.050000	0	1.000	1.000	New, 7F4854
358	P	Turkey- lean/fat free w/o bones	0.050000	0	1.000	1.000	New, 7F4854
449	P	Turkey-other organ meats	0.100000	0	1.000	1.000	New, 7F4854
398	D	Milk-based water	0.200000	0	1.000	1.000	P
319	D	Milk-fat solids	0.200000	0	1.000	1.000	P
318	D	Milk-nonfat solids	0.200000	0	1.000	1.000	P
320	D	Milk sugar (lactose)	0.200000	0	1.000	1.000	P
303	6A	Soybean-other	6.700000	0	1.000	0.020	New, 3 ppm + 18 ppm, 7F04854, AR
307	6A	Soybeans-flour (defatted)	1.900000	0	1.000	0.020	New, 3 ppm + 18 ppm, 7F04854, AR
306	6A	Soybeans-flour (low fat)	1.9 0000	0	1.000	0.020	New, 3 ppm + 18 ppm, 7F04854, AR
305	6A	Soybeans-flour (full fat)	1.900000	0	1.000	0.020	New, 3 ppm + 18 ppm, 7F04854, AR
304	6A	Soybeans-mature seeds dry	6.700000	0	1.000	0.020	New, 3 ppm + 18 ppm, 7F04854, AR
297	6A	Soybeans-oil	1.900000	0	1.000	0.020	New, 3 ppm + 18 ppm, 7F04854, AR
255	6A	Soybeans-sprouted seeds	6.700000	0	0.330	0.020	New, 3 ppm + 18 ppm, 7F04854, AR
20	10	Citrus citron	0.050000	0	1.000	1.000	0F3890
23	10	Grapefruit-juice	0.050000	0	2.100	0.160	0F3890
441	10	Grapefruit-juice-concentrate	0.050000	0	8.260	0.160	0F3890
448	10	Grapefruit peel	0.050000	0	1.000	0.160	0F3890

22	10	Grapefruit-peeled fruit	0.050000	0	1.000	0.160	0F3890
24	10	Kumquats	0.050000	0	1.000	1.000	0F3890
28	10	Lemons-juice	0.050000	0	2.000	1.000	0F3890
442	10	Lemons-juice-concentrate	0.050000	0	11.400	1.000	0F3890
27	10	Lemons-peel	0.050000	0	1.000	1.000	0F3890
26	10	Lemons-peeled fruit	0.050000	0	1.000	1.000	0F3890
32	10	Limes-juice	0.050000	0	2.000	1.000	0F3890
443	10	Limes-juice-concentrate	0.050000	0	6.000	1.000	0F3890
31	10	Limes-peel	0.050000	0	1.000	1.000	0F3890
30	10	Limes-peeled fruit	0.050000	0	1.000	1.000	0F3890
36	10	Oranges-juice	0.050000	0	1.800	0.040	0F3890
33	10	Oranges-juice-concentrate	0.050000	0	6.700	0.040	0F3890
35	10	Oranges-peel	0.050000	0	1.000	0.040	0F3890
34	10	Oranges-peeled fruit	0.050000	0	1.000	0.040	0F3890
37	10	Tangelos	0.050000	0	1.000	1.000	0F3890
38	10	Tangerines	0.050000	0	1.000	1.000	0F3890
39	10	Tangerines-juice	0.050000	0	2.300	1.000	0F3890
420	10	Tangerines-juice-concentrate	0.050000	0	7.350	1.000	0F3890
52	11	Apples	0.050000	0	1.000	1.000	Pend, 0F04554
53	11	Apples-dried	0.050000	0	8.000	1.000	Pend, 0F04554
54	11	Apples-juice/cider	0.050000	0	1.300	1.000	Pend, 0F04554
377	11	Apples-juice-concentrate	0.050000	0	3.900	1.000	Pend, 0F04554
55	11	Crabapples	0.050000	0	1.000	1.000	Pend, 0F04554
81	11	Loquats	0.050000	0	1.000	1.000	Pend, 0F04554
56	11	Pears	0.050000	0	1.000	1.000	Pend, 0F04554
57	11	Pears-dried	0.050000	0	6.250	1.000	Pend, 0F04554
404	11	Pears-juice	0.050000	0	1.000	1.000	Pend, 0F04554
58	11	Quinces	0.050000	0	1.000	1.000	Pend, 0F04554
410	12	Apricot juice	0.050000	0	1.000	1.000	P, 3F4238
59	12	Apricots	0.050000	0	1.000	1.000	P, 3F4238
60	12	Apricots-dried	0.050000	0	6.000	1.000	P, 3F4238
61	12	Cherries	0.050000	0	1.000	1.000	P, 3F4238
62	12	Cherries-dried	0.050000	0	4.000	1.000	P, 3F4238
63	12	Cherries-juice	0.050000	0	1.500	1.000	P, 3F4238
64	12	Nectarines	0.050000	0	1.000	1.000	P, 3F4238
65	12	Peaches	0.050000	0	1.000	0.010	P, 3F4238
66	12	Peaches-dried	0.050000	0	7.000	0.010	P, 3F4238
402	12	Peaches-juice	0.050000	0	1.000	0.010	P, 3F4238
67	12	Plums (damsons)	0.050000	0	1.000	1.000	P, 3F4238
68	12	Plums-prunes (dried)	0.200000	0	1.000	1.000	P, 3F4238
69	12	Plums/prune-juice	0.200000	0	1.000	1.000	P, 3F4238
40	14	Almonds	0.050000	0	1.000	1.000	P, 4F4343
51	14	Beechnuts	0.050000	0	1.000	1.000	P, 4F4343
41	14	Brazil nuts	0.050000	0	1.000	1.000	P, 4F4343
49	14	Butter nuts	0.050000	0	1.000	1.000	P, 4F4343

42	14	Cashews	0.050000	0	1.000	1.000	P, 4F4343
43	14	Chestnuts	0.050000	0	1.000	1.000	P, 4F4343
44	14	Filberts (hazelnuts)	0.050000	0	1.000	1.000	P, 4F4343
45	14	Hickory nuts	0.050000	0	1.000	1.000	P, 4F4343
46	14	Macadamia nuts (bush nuts)	0.050000	0	1.000	1.000	P, 4F4343
47	14	Pecans	0.050000	0	1.000	1.000	P, 4F4343
431	14	Walnut oil	0.050000	0	1.000	1.000	P, 4F4343
48	14	Walnuts	0.050000	0	1.000	1.000	P, 4F4343
267	15	Corn grain-bran	0.200000	0	1.000	0.010	P
266	15	Corn grain-endosperm	0.200000	0	1.000	0.010	P
289	15	Corn grain-oil	0.200000	0	1.000	0.010	P
268	15	Corn grain/sugar/hfcs	0.200000	0	1.500	0.010	P
388	15	Corn grain/sugar-molasses	0.200000	0	1.500	0.010	P
237	15	Corn/pop	0.200000	0	1.000	0.010	P
278	15	Wheat-bran	2.500000	0	1.000	0.010	Pend, 0F04554
279	15	Wheat-flour	0.750000	0	1.000	0.010	Pend, 0F04554
277	15	Wheat-germ	0.750000	0	1.000	0.010	Pend, 0F04554
437	15	Wheat-germ oil	0.750000	0	1.000	0.010	Pend, 0F04554
276	15	Wheat-rough	0.750000	0	1.000	0.010	Pend, 0F04554

Attachment 4: Chronic Exposure Analysis

U.S. Environmental Protection Agency Ver. 6.74
DEEM Chronic analysis for SULFOSATE (1989-92 data)
Residue file name: C:\deem\resdata\128501c.R96 Adjustment factor #2 used.
Analysis Date 04-22-1999/07:40:07 Residue file dated: 04-22-1999/07:39:18/8
Reference dose (RfD, CHRONIC) = .0333 mg/kg bw/day
COMMENT 1: aPAD of 0.333 mg/kg/d and c PAD of 0.0333 mg/kg/d includes (10x inter, 10x intra, 3x FQPA); ARs used

Total exposure by population subgroup

Population Subgroup	Total Exposure mg/kg body wt/day	Total Exposure Percent of Rfd
U.S. Population (total)	0.003078	9.2%
U.S. Population (spring season)	0.003045	9.1%
U.S. Population (summer season)	0.003058	9.2%
U.S. Population (autumn season)	0.003161	9.5%
U.S. Population (winter season)	0.003046	9.1%
Northeast region	0.003037	9.1%
Midwest region	0.003353	10.1%
Southern region	0.002977	8.9%
Western region	0.002962	8.9%
Hispanics	0.003346	10.0%
Non-hispanic whites	0.003056	9.2%
Non-hispanic blacks	0.003010	9.0%
Non-hisp/non-white/non-black)	0.003194	9.6%
All infants (< 1 year)	0.004420	13.3%
Nursing infants	0.001401	4.2%
Non-nursing infants	0.005690	17.1%
Children 1-6 yrs	0.008682	26.1%
Children 7-12 yrs	0.005057	15.2%
Females 13-19(not preg or nursing)	0.002643	7.9%
Females 20+ (not preg or nursing)	0.001864	5.6%
Females 13-50 yrs	0.002066	6.2%
Females 13+ (preg/not nursing)	0.002620	7.9%
Females 13+ (nursing)	0.002597	7.8%
Males 13-19 yrs	0.003313	9.9%
Males 20+ yrs	0.002216	6.7%
Seniors 55+	0.001899	5.7%
Pacific Region	0.002933	8.8%